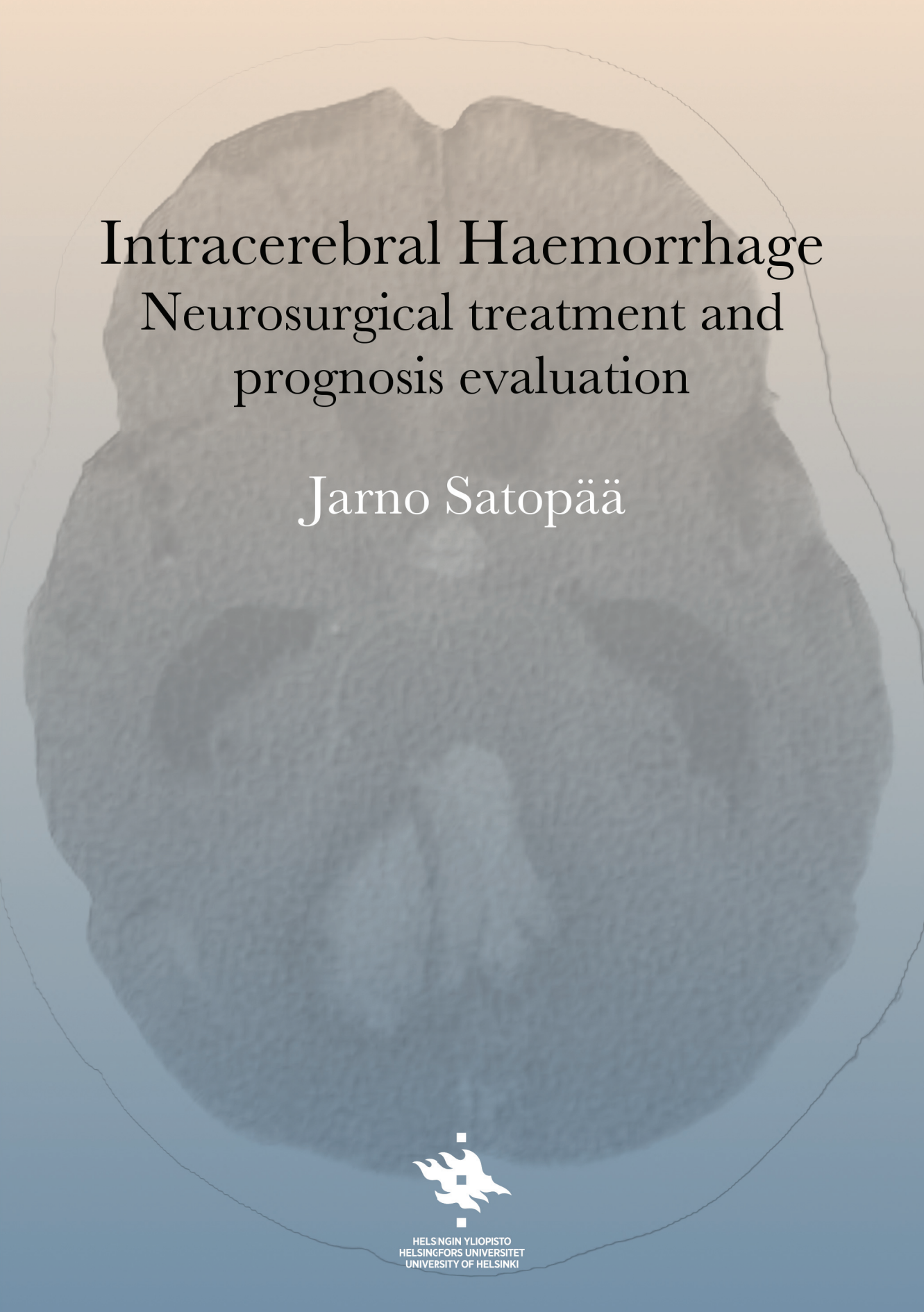

Intracerebral Haemorrhage
Neurosurgical treatment and prognosis evaluation

Jarno Satopää

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

Intracerebral haemorrhage: Neurosurgical treatment and prognosis evaluation

Jarno Satopää

Department of Neurosurgery
Helsinki University Hospital

Clinical Neurosciences, Neurosurgery

University of Helsinki

Doctoral School in Health Sciences
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Supervisors
Professor Mika Niemelä
Department of Neurosurgery
Helsinki University Hospital
Department of Clinical Neurosciences, Neurosurgery
University of Helsinki

Adjunct Professor Jukka Putaala
Department of Neurology
Helsinki University Hospital
Department of Clinical Neurosciences, Neurology
University of Helsinki

Reviewers
Adjunct Professor Sami Tetri
Department of Neurosurgery
Oulu University Hospital
Oulu, Finland

Professor Eivind Berge
Director of Stroke Research Group
Department of Cardiology
Oslo University Hospital
Oslo, Norway

Opponent
Professor A. David Mendelow
Department of Neurosurgery and the Institute of Neuroscience
University of Newcastle upon Tyne
Newcastle upon Tyne, United Kingdom

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Author's contact information:

Jarno Satopää
Department of Neurosurgery
Helsinki University Hospital
Topeliuksenkatu 5 B
00029 Helsinki
FINLAND
mobile: +358-(0)50-428 6743
fax: +358-(0)9-471 87560
email: jarno.satopaa@fimnet.fi

TABLE OF CONTENTS

ABSTRACT

Intracerebral haemorrhage (ICH) is a deadly subtype of stroke with an average 12-month mortality exceeding 50%. The most common causes for ICH include hypertensive microangiopathy, amyloid angiopathy, antithrombotic or anticoagulant medication, or systemic diseases. Despite advances at other frontiers of stroke treatment, treatment options for ICH are limited. Neurosurgical treatment for ICH has been discussed in recent multicentre studies, but no definitive answer of its utility has emerged. Age, ICH volume and location, and extent of ventricular haemorrhage among other factors affect the prognosis after ICH. We studied the different prognostic scores for ICH to find the best tool for estimation of the risk of death after ICH. One of the best known is the ICH score, published in 2001. In addition, we studied the effect of neurosurgical treatment (1) in patients with intracerebellar haemorrhage; (2) in patients with ICH-related hydrocephalus; and (3) in young adults in an observational, retrospective analysis of consecutive ICH patients admitted to Helsinki University Hospital during a five-year period. Traumatic and aneurysmal ICHs were excluded from the study.

We found 19 prognostic scores, many of which were based on the original ICH score. For estimating the risk of in-hospital death, the National Institutes of Health Stroke Scale performed as well as the best dedicated scores. For 3- and 12-month mortality, the ICH Functional Outcome Scale (ICH-FOS) performed best. However, all prognostic scores share the risk of self-fulfilling prophecies, the estimated poor outcome resulting in limitations of care.
Based on a mutual consensus among neurologists and neurosurgeons, cerebellar ICH is usually treated surgically in patients with a declining level of consciousness and a large haematoma. However, in our series, surgical and medical treatment did not differ in short- or long-term mortality, but surgically treated patients were left in a poor clinical condition at hospital discharge. The surgically treated patients were younger, had larger ICHs and their level of consciousness on arrival was lower than the conservatively treated patients. Although surgically treated patients were left in a poor condition, no data exist on long-term functional outcome and recovery after intracerebellar haemorrhage. More studies are needed.

ICH-related hydrocephalus is usually considered a predictor of poor outcome. In our series, hydrocephalic patients had very high mortality, but surgical treatment – either by external ventricular drainage or evacuation of a hydrocephalus-causing cerebellar ICH – was associated with lower in-hospital and 3-month mortality. Only a small subgroup of all hydrocephalic patients received surgical treatment, but a difference in mortality between surgically and conservatively treated patients was observed in a propensity-matched case-control comparison. The high mortality previously attributed to ICH-related hydrocephalus may be a self-fulfilling prophecy.

ICH in the young was caused most often by hypertension and structural vascular anomalies such as arteriovenous malformations or cavernous angiomas. The predictors of poor outcome did not differ from those in older patients, these being Glasgow coma score < 8, infratentorial location, intraventricular blood, hydrocephalus, and haematoma volume > 30 ml. However, surgical treatment was associated with significantly lower mortality than conservative treatment.

In conclusion, surgical treatment was associated with a lower short- and long-term mortality in patients with ICH-related hydrocephalus and in young adults. More studies are needed to elucidate the advantages and disadvantages of surgical treatment in patients with intracerebellar haemorrhage and ICH-related hydrocephalus.

TIIVISTELMÄ

Aivojensisäisen verenvuodon kirurginen hoito ja ennuste

Tutkimuksen taustaa

Aivojensisäinen verenvuoto on äkillinen ja tappava sairaus, johon sairastuneista yli puolet menehtyy vuoden sisällä. Vuodon tavallisimpia syitä ovat hitaasti kehittyvät rappeumamuutokset aivojen pienissä valtimoissa esimerkiksi verenpainetaudin seurauksena ja veren hyytymiseen vaikuttavat lääkkeet. Aivojen sisällä verihyytymä vaurioittaa aivokudosta paikallisesti repien harmaan ja valkean aineen hermoratoja, kun taas veren aiheuttama kemiallinen ärsytys ja painevaikutus aiheuttavat lisävaurioita sitä ympäröiviin rakenteisiin.

Aivojensisäisen verenvuodon ennuste riippuu vuodon sijainnin ja koon lisäksi potilaan iästä, taustasairauksista ja aiemmasta lääkityksestä. Ennusteen arviointiin on kehitetty lukuisia pisteytysmalleja. Leikkaushoidon vaikutusta kuolleisuuteen on aiemmin selvitetty laajoissa satunnaistetuissa monikeskustutkimuksissa, eikä kiistatonta näyttöä sen hyödyistä ole saatu. Leikkaushoitoa kuitenkin harkitaan nuorilla potilailla sekä silloin, kun hyytymä sijaitsee pikkuaivoissa ja painaa aivorunkoa tai tukkii aivo-selkäydinnestekierron.

Tutkimuksen toteutus

Tässä väitöskirjassa tutkittiin aivojensisäisen verenvuodon hoitotuloksia Helsingin yliopistollisessa keskussairaalassa vuosina 2005-2010 yli tuhannen potilaan aineistossa, keskittyen kirurgisesti hoidettuihin potilasryhmiin: pikkuaivovuodon saaneisiin potilaisiin, nuoriin aikuispotilaisiin ja niihin, joille kehittyi vuodon seurauksena aivo-selkäydinnestekierron häiriö eli hydrokefalus. Lisäksi tutkimme, mikä olemassa olevista 19 pisteytysmallista ennustaa parhaiten vuodonjälkeistä kuolleisuutta. Kyseessä oli takautuva asiakirjatutkimus.

Tutkimuksen tulokset

Totesimme, että pikkuaivovuodon kirurgisen hoidon tulokset olivat odotettua heikommat – leikattujen ja lääkkeellistä tuki- ja tehohoitoa saaneiden potilaiden kuolleisuus oli yhtä suurta. Leikkauksen ansiosta osa todennäköisesti jäi henkiin, mutta huonokuntoisiksi jääneiden vuodepotilaiden osuus oli leikattujen potilaiden ryhmässä merkittävästi suurempi. Tuloksemme vahvistavat viimeaikaisia havaintoja, joiden mukaan pikkuaivovuodon leikkaushoito ei ole niin hyödyllistä kuin yleensä ajatellaan.

Kuolleisuus oli erittäin runsasta myös niillä potilailla, joille kehittyi vuodon seurauksena aivo-selkäydinnestekierron häiriö. Aiempien tutkimusten perusteella arvelimme, että leikkaushoito ei merkittävästi parantaisi ennustetta. Leikattujen potilaiden kuolleisuus oli kuitenkin yllättäen merkittävästi pienempää kuin lääkkeellistä teho- ja tukihoitoa saaneilla potilailla.

Myös nuorten aikuispotilaiden leikkaushoito vuodon sijainnista riippumatta paransi ennustetta lääkkeellistä tuki- ja tehohoitoa saaneisiin potilaisiin verrattuna. Pisteytysmalleista totesimme, että aivoverenkiertohäiriön vaikeusasteen arviointiin tarkoitettu National Institutes of Health Stroke Scale (NIHSS) ennusti parhaiten sairaalassa tapahtuvaa kuolleisuutta, kun taas kolmen kuukauden ja vuoden kuluttua vuodosta kuolleisuutta ennusti parhaiten tähän tarkoitukseen kehitetty ICH Functional Outcome Score (ICH-FOS).

Loppupäätelmät

Aivojensisäisen verenvuodon leikkaushoidon tulokset Helsingin yliopistollisessa keskussairaalassa olivat odotettua paremmat nuorilla

aikuisilla vuodon sijainnista riippumatta sekä niillä potilailla, joilla vuoto aiheutti aivo-selkäydinnestekierron häiriön. Pikkuaivovuodon saaneilla potilailla taas leikkauksen hyödyt jäivät odotettua pienemmiksi. Hoitovaihtoehtoja tulee arvioida kaikilla aivojensisäisen verenvuodon saaneilla potilailla yksilöllisesti ja harkita leikkaushoitoa niillä potilailla, joiden toipumisennustetta se todennäköisimmin parantaa.

ABBREVIATIONS

AD	Alzheimer disease
AHA	American Heart Association
APOE	Apolipoprotein E
ASA	American Stroke Association
AUC	Area under curve
AVF	Arteriovenous fistula
AVM	Arteriovenous malformation
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CSF	Cerebrospinal fluid
CSVD	Cerebral small vessel disease
CT	Computerised tomography
CTA	Computerised tomography angiography
dAVF	Dural arteriovenous fistula
DC	Decompressive craniectomy
ESO	European Stroke Organisation
EVD	External ventricular drainage
GCS	Glasgow Coma Scale
Hb	Haemoglobin
HR	Hazard ratio
HUH	Helsinki University Hospital
ICD-10	International Classification of Diseases, 10th version
ICH	Intracerebral haemorrhage
IQR	Interquartile range
IS	Ischaemic stroke
IVH	Intraventricular haemorrhage
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
ROC	Receiver operating curve
RR	Relative risk
rTPA	Recombinant tissue plasminogen activator
SAH	Subarachnoid haemorrhage
SD	Standard deviation

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their Roman numerals:

I Satopää J, Mustanoja S, Meretoja A, Putaala J, Kaste M, Niemelä M, Tatlisumak T, Strbian D. Comparison of all 19 published scores for intracerebral hemorrhage. *J Neurol Sci:* 2017;379;103-108.

II Satopää J, Meretoja A, Koivunen R, Mustanoja S, Putaala J, Kaste M, Strbian D, Tatlisumak T, Niemelä M. Treatment of intracerebellar haemorrhage: poor outcome and high long-term mortality. *Surg Neurol Int*: 2017, in press.

III Satopää J, Meretoja A, Koivunen R, Mustanoja S, Kaste M, Strbian D, Tatlisumak T, Niemelä M, Putaala J. Hydrocephalus caused by intracerebral hemorrhage: Patients benefit from surgical treatment. *Manuscript*

IV Koivunen R, Satopää J, Haapaniemi E, Strbian D, Meretoja A, Mustanoja S, Silvennoinen H, Salonen O, Niemelä M, Tatlisumak T, Putaala J. Predictors of Early Mortality in Young Adults After Intracerebral Hemorrhage. *Stroke*: 2014;45;2454-2456. *(Courtesy of Dr. Riku Koivunen; the manuscript was also used as an original publication in the doctoral thesis of Dr. Riku Koivunen "Intracerebral hemorrhage in the young", University of Helsinki, 2015)*

1 INTRODUCTION

Intracerebral haemorrhage (ICH) is a deadly subtype of stroke with an average 12-month mortality exceeding 50%.[1] The bleeding can be caused by a structural, macrovascular lesion such as cerebral artery aneurysm or arteriovenous malformation (AVM). However, the majority of ICHs are microvascular, also called "primary" or "spontaneous", originating from the small deep cerebral vessels.[2] The most common causes for ICH include hypertensive microangiopathy, amyloid angiopathy, antithrombotic or anticoagulant medication, or systemic diseases such as liver cirrhosis.[3]

The key to minimising stroke-related mortality and morbidity is prevention – calculations from the Global Burden of Disease study show that 2/3 of all cerebral strokes could be prevented.[4] Key targets for primary stroke prevention are blood pressure lowering, smoking cessation, treatment with anticoagulant medication in patients with atrial fibrillation, daily aspirin and statin treatment in high-risk individuals, and screening for carotid artery stenosis in patients suffering a transient ischaemic attack (TIA).[5]

Sometimes prevention fails and a cerebral stroke occurs. Recent years have seen an increase in treatment possibilities for ischaemic stroke (IS), where thrombolysis and intra-arterial treatments have become routine, at least in specialist acute stroke centres.[6] However, in acute ICH, scientifically proven treatment options are limited. The current guidelines support rapid neuroimaging, medical treatment of clinical seizures, blood pressure lowering, treatment in specialist acute stroke unit, use of intermittent pneumatic stockings to prevent deep venous thrombosis, and multidisciplinary rehabilitation.[7,8]

The American Stroke Association (ASA) guidelines for the treatment of ICH also encourage the use of clinical prognostic scores as a routine part of evaluation.[7] The most widely used prognostic score is the ICH score.[9] However, after its publication in 2001, prognostic scores have become hugely popular, with nearly 20 scores since published. These have rarely been compared with each other.

Since the 1960s, surgical treatment of ICH has been considered controversial, especially in comatose patients.[10] In 1989, a randomised controlled study was performed at the Helsinki University Hospital on surgical treatment of deep ICH. The study showed that the surviving patients were left in very poor condition.[11] Newer, randomised studies have also failed to show substantial benefit from surgical treatment of ICH.[11-14] However, a subgroup of ICH patients routinely undergoes surgical treatment, namely patients with cerebellar ICH; there has been a wide mutual consensus in the neurological and neurosurgical communities that cerebellar ICHs should be operated. Nevertheless, the scientific proof is mainly based on small retrospective series with conflicting results.[15] To relieve brainstem compression and hydrocephalus, surgeons tend to favour surgical treatment in patients with a declining level of consciousness.[16] Some regard this as counterintuitive, as the results on long-term outcome after surgery of cerebellar ICH are generally pessimistic.[17]

Intraventricular haemorrhage (IVH) and hydrocephalus also often require neurosurgical attention. ICH-related acute hydrocephalus and IVH have been found to be strong and independent predictors of poor functional outcome and mortality.[18] Traditionally, acute hydrocephalus has been considered an indication for surgery in patients with a cerebellar ICH[19], although strong evidence to support treatment of hydrocephalus in other types of ICH is virtually absent.[20] IVH has been studied extensively, but there are no randomised studies on the treatment of ICH-related hydrocephalus.

We set out to study those subgroups of ICH patients that are most often encountered by the practicing neurosurgeon: patients with a cerebellar ICH or ICH-related hydrocephalus and young patients. Our objectives were to assess the different outcome-modifying factors behind the prognostic scores for ICH, and the prognostic performance of the different scores in a large, external cohort of consecutive patients. We also studied the long-term and functional outcome after evacuation of cerebellar ICH, and the mortality after surgical treatment of ICH-related acute hydrocephalus. In addition, we investigated the effect of surgical treatment on mortality in young (16 to 49 years) patients with ICH.

2 REVIEW OF THE LITERATURE

2.1 Intracerebral haemorrhage (ICH)

2.1.1 Definition

Intracerebral haemorrhage (ICH) is defined as a focal collection of blood inside the brain parenchyma or the brain ventricles that is not caused by trauma.[21] ICH can originate from structural or macrovascular structures, namely brain tumours, cerebral artery aneurysms, arteriovenous malformations (AVM), dural arteriovenous fistulae (dAVF), or cavernous angiomas.[22] The majority of ICHs are, however, caused by microangiopathic, i.e. degenerative changes in deep cerebral arterioles.[2] Intraparenchymal haemorrhages from arterial aneurysms were excluded from this literature review because of major differences in their pathogenesis, age distribution, and treatment.

2.1.2 Epidemiology

ICH constitutes around 9-27% of all types of stroke.[23-25] Globally, the incidence of haemorrhagic stroke (ICH and aneurysmal SAH) has increased by 47% between 1990 and 2010.[26] While the number of patients with SAH has remained stable or even decreased in the last years, the ICH incidence has increased globally in low-income countries, probably due to the increasing prevalence of hypertension and smoking.[23,27] The global mean overall incidence of ICH was 24.6 per 100 000 person-years, varying markedly between different racial and age groups. The incidence was similar in white, black, Hispanic, and Maori people but two times higher (incidence ratio 2.1) in South and Southeast Asian people.[1]

Age had a major influence in the incidence, ranging from 1.9/100 000 person-years in patients under 45 years to 196/100 000 in patients over 85 years.[1] In the Finnish population, incidence has varied between 2/100 000 in patients under 39 years and 222/100 000 in patients over 80 years.[28] The mean age of Finnish ICH patients was 69.5 years [29], and the total incidence has ranged from 17 to 35/100 000 person-years.[28,30,31]

Globally, although age-standardised stroke mortality has decreased, the incidence and overall disease burden caused by stroke have increased – especially in low- and middle-income countries.[26] Noteworthy is that while the absolute number of ischaemic strokes (ISs) was twice that of haemorrhagic strokes the majority of the disease burden (deaths and disease-affected life-years, DALYs) was caused by haemorrhagic stroke, mainly in the low- and middle-income countries.[32] Socio-economic status also affected the ICH incidence in a Finnish population – Jakovljevic and colleagues[33] noted that the age-standardised incidence of first-ever ICH was approximately three times higher in men and four times higher in women in the low-income group than in the high-income group.

In American urban teaching hospitals, the hospital admission rates for stroke have increased between 1990-1991 and 2000-2001. The increase in admissions was 19% for ICH patients, while the overall in-hospital mortality decreased by 6%, from 29.9% to 28.1%. Ischaemic stroke admissions rose by 13%, while the in-hospital mortality decreased by 36%, from 8.3% to 5.3%.[34] The increase in admissions is probably caused by epidemiological transition: greater number of elderly people and increases in the risk factors in the poor.[35] While the acknowledgement and treatment of risk factors for cardiovascular disease and recent advances in acute treatment options have reduced the mortality after IS in high-income countries, mortality after ICH remains quite high, both in high-income and in low-income countries.[32,35] In a recent global meta-analysis, one-year survival after ICH was

as low as 46%, and 5-year survival strikingly low, 29%.[36] In a single-centre follow-up study, mortality at 7 days, 1 year, and 10 years was 31%, 59%, and 82%, respectively.[37]

2.1.3 Aetiology

2.1.3.1 Hypertensive microangiopathy

The most common cause of ICHs is hypertensive microangiopathy, causing 35-60% of all ICHs.[3,38] Hypertension, defined as > 140 mmHg systolic or > 90 mmHg diastolic blood pressure [39], causes degenerative changes in the walls of perforating small arterioles, originating from the anterior, middle, or posterior cerebral arteries or the basilar artery. Continuously increased pressure in the arterioles damages the vessel walls and reduces vessel wall compliance.[22] The original hypothesis by Charcot and Bouchard in 1868 was that hypertension would cause the formation of small miliary or microaneurysms in the walls of these small arterioles. Studies have since shown that the affected vessels have marked medial smooth muscle layer atrophy coexisting with atherosclerosis, giving them the typical moth-eaten appearance, and the rupture site is usually in a vessel bifurcation in the distal lenticulostriate arteries.[40,41]

Hypertensive microangiopathy is a part of a larger vasculopathic phenomenon, cerebral small vessel disease (CSVD).[42] In radiologic studies, CSVD presents as subcortical and periventricular white matter hyperintensities [43], lacunar infarcts [44], and cerebral microbleeds .[45] CSVD can cause a broad spectrum of symptoms. It has been associated with gait problems and incontinence [46], cognitive decline [47], and depression [48], and it may also contribute to the development of Alzheimer's disease.[49] Hypertension-related ICHs are most often consid-

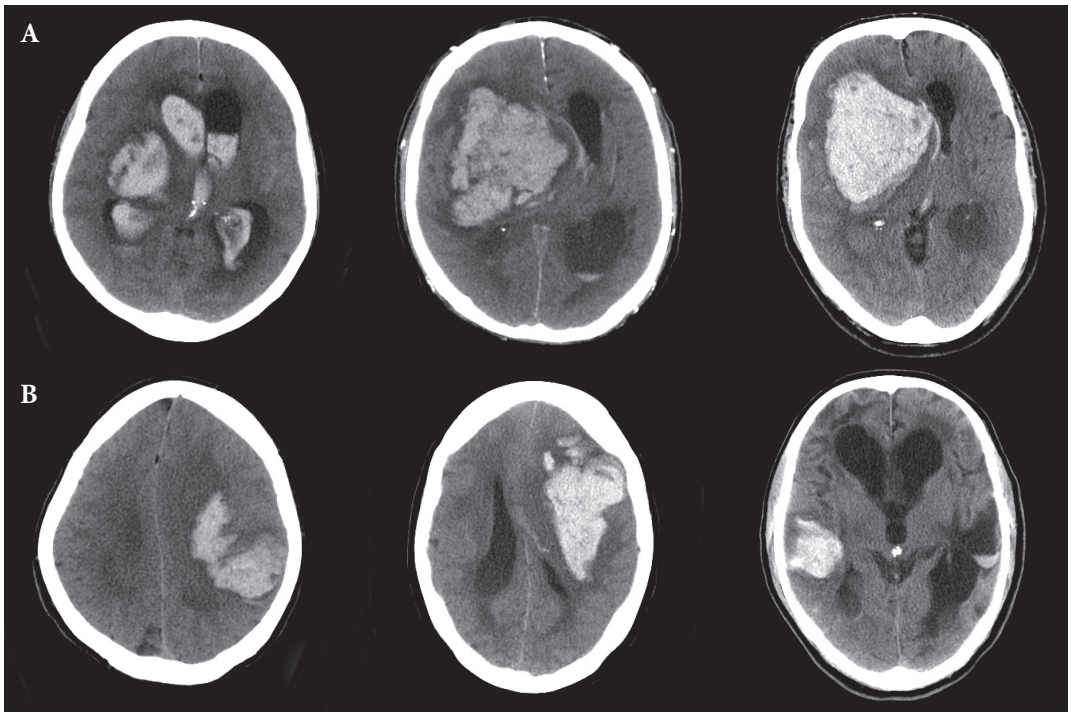


Figure 1. Examples of ICHs related to hypertensive microangiopathy or amyloid angiopathy in axial brain CT. (A) Hypertensive ICHs are often located in the deep brain structures, i.e. thalamus, basal ganglia, or internal capsule. (B) Intracerebral haemorrhages caused by amyloid angiopathy are, in contrast, often located cortically and may include multiple foci.

ered to be located in the basal ganglia and thalamic regions.[50,51] History of hypertension was often present in patients with a lobar or a deep ICH, in 48-56% and 68-70%, respectively.[3,38]

2.1.3.2 Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is the second most common cause for ICH, responsible for about 20% of all ICHs and up to 80% of lobar ICHs.[3,52] CAA causes deposition of beta-amyloid, formation of microaneurysms, and hyalinoid necrosis in the walls of small leptomeningeal and cortical arteries that can lead to vessel rupture and haemorrhage.[53] It has been recently shown that the degree of dilation in the juxtacortical perivascular spaces predicts the severity of CAA.[54] Other biomarkers associated with CAA visible on magnetic resonance imaging (MRI) or tissue specimens are white matter hyperintensities, solely lobar cerebral microbleeds, and cortical superficial siderosis, i.e. deposition of haemosiderin in cortical sulci visible in MRI.[55-57] Also apolipoprotein E (APOE) epsilon (ε) 2 and 4 genotypes have been associated with the vascular changes seen in CAA.[58,59]

Traditionally, CAA has been diagnosed from post-mortem or operative tissue specimens with "Congo red" staining. It is a rather usual finding in the post mortem brain specimens of the elderly with a frequency ranging up to 36% and 46% in over 60-year-old and over 70-year-old patients, respectively.[60] However, tissue samples are somewhat impractical and hard to obtain – especially because a clinical diagnosis of a probable CAA has traditionally been considered a contraindication for surgical treatment due to difficulties in achieving postoperative haemostasis.[61] However, in those patients that undergo surgical biopsy or post-mortem autopsy, CAA can be reliably diagnosed in a small biopsy specimen.[62] It has also been suggested that decreased levels of beta-amyloid in cerebrospinal fluid (CSF) would serve as a preclinical biomarker for developing CAA.[63]

The Boston classification was developed to aid the diagnosis of CAA on a clinical basis and it helps dividing patients into the categories of possible, probable, and definite CAA. The criteria state that even without a tissue specimen, CAA is probable in patients ≥ 55 years, with imaging findings of multiple cortical, subcortical, or subcorticocortical haemorrhages in the absence of other causes of haemorrhage.[52] However, autopsy studies have shown that in sporadic amyloid angiopathy, the incidence of ICHs was surprisingly low, in the range of 5.4-7.6%.[64,65] Non-haemorrhagic and haemorrhagic CAA have been suggested to be linked to the different APOE genotypes – APOE ε2 genotype seemed to be associated with vasculopathy leading to haemorrhage, while APOE ε4 was associated with the deposition of amyloid in the vessel walls.[55] In addition, CAA often coexists with Alzheimer disease (AD) – up to 95% of patients with AD had CAA findings in autopsy samples. It has been demonstrated that the beta-amyloid peptide found in vessel walls in CAA and senile plaques in AD is essentially similar.[66]

Together, hypertensive microangiopathy and CAA account for around 55% of all ICHs.[3] However, as most ICH patients do not undergo MRI to reveal the location of possible microbleeds and biopsy specimens are rarely available, the distinction between these two is somewhat unreliable. In patients diagnosed with "possible" CAA as per the Boston criteria, 38% of patients were shown not to have CAA-related changes in autopsy specimens.[52]

2.1.3.3 ICH related to macro-vascular structural anomalies

Many macroscopic vascular and structural anomalies or diseases, such as brain arteriovenous malformations (AVMs), dural arteriovenous fistulae (dAVF), and cavernous angiomas, also known as cavernomas, can cause intracerebral haemorrhage (Figure 2). Cerebral artery aneurysms can also cause an ICH, but because of the great differences in the

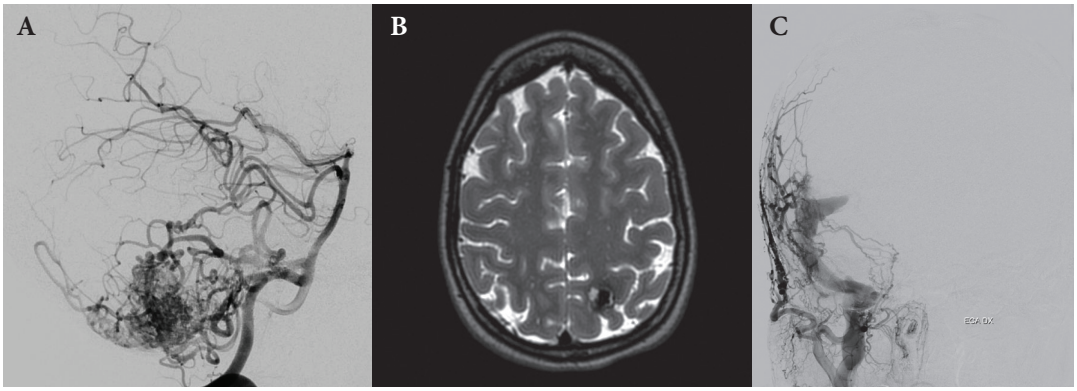


Figure 2. Different types of structural causes for ICH. (A) A cerebellar AVM filling from superior, anterior inferior and posterior inferior cerebellar arteries in a digital subtraction angiography (DSA) image, vertebral artery injection, sagittal view. (B) A small, cortical, cavernous angioma in the parietal lobe of the left hemisphere in an axial T2-weighted MRI. (C) A large dAVF in the right occipital region. The fistula is fed by the external carotid artery and it drains to the right transverse and sigmoid sinuses. Coronal view of a DSA, right external carotid artery injection.

presentation, outcome and treatment, these have intentionally been omitted from this literature review.

AVMs have been thought to be congenital and be formed in the embryonic phase,[67] during foetal development, or after birth.[68] They consist of a feeding artery, a tangle of anomalous blood vessels that allow rapid blood flow between the artery and vein structures (nidus), and a draining vein.[69] In the brain, the anomalous arteries lack a smooth muscle layer, while the anomalous veins have fibrous thickening of the vessel walls.[70] The anomalous vessels or aneurysms related to the high flow through the AVM may rupture and cause an ICH.[71] While no single causative factor has been found, an epigenetic underlying mechanism has been proposed.[72] A recent study also suggested that single-nucleotide polymorphisms in the NOTCH4 gene could be associated with the development of AVMs.[73]

The estimated annual rupture risk in all AVMs is estimated to be 2.5-4.6%, being highest in large, deep-seated, infratentorial, or previously ruptured AVMs with associated aneurysms.[71,74] Because of the rupture risk, AVMs can be treated by surgery, endovascular embolization, irradiation, or conservative management.[75] In long-term follow-up, especially conservatively treated AVMs seem to carry a high risk of excess mortality relative to the non-affected population [76], although treatment of unruptured AVMs has also been associated with an increased risk of poor outcome.[77-79] However, compared with other ICH aetiologies, patients with an AVM-related haemorrhage seem to have a higher chance of good recovery.[80]

Dural arteriovenous fistulae are another type of vascular malformation of the brain sometimes responsible for an ICH. Contrary to AVMs, dural arteriovenous fistulae are thought to be mainly acquired lesions and occur usually in the vicinity of dural sinuses.[81] They may be formed after cerebral venous sinus thrombosis, trauma, or intracranial surgery, but the underlying mechanism has not been established.[82] The anomalous connections form between the branches of dural or pial arteries and venous structures.[83] They have a risk of intracranial haemorrhage if the venous outflow is directed through the cortical veins.[84]

Brain cavernous angiomas are benign, vascular formations of dilated capillaries in the brain tissue that lack the normal vascular morphology, usually with a haemosiderin-rich layer in the surrounding brain tissue.[85] They are thought to form in the embryonic phase, but recent studies have shown growth by vascular proliferation and neoangiogenesis of cavernous angiomas in adult patients.[86] After irradiation, *de novo* lesions with a similar histopathological appearance have also been observed.[87]

Cavernous angiomas can reside anywhere in the central nervous system[88] and be sporadic or hereditary.[89] They often present with an epileptic seizure[90], and the 5-year risk of subsequent epilepsy may be as high as 94%.[91] A cavernous angioma may bleed and cause a subclinical haemorrhage, acute massive haemorrhage, or slow oozing of red blood cells through the capillary walls.[87] The risk of haemorrhage depends on the location and initial presentation, being highest in cavernous angiomas situated in deep, infratentorial or spinal locations.[92,93] The 5-year risk of haemorrhage has been estimated between 2.4% and 3.8% in patients without initial ICH and 29.5% to 30.8% in patients with a previously bleeding cavernous angioma.[93,94]

Surgical treatment has been suggested for cavernous angiomas that have previously ruptured to minimise the risk of re-rupture[95] and for those causing symptomatic epilepsy.[90] In surgery, it is considered important to remove not only the vascular malformation, but also the surrounding haemosiderin-rich rim because of its epileptogenicity.[90,92,96] The outcomes after surgery are usually considered good.[90] However, in a recent prospective observational study, surgical treatment of cavernous angiomas was associated with a worse functional 5-year outcome than conservative management.[97]

2.1.4 General pathophysiology of ICH

The immediate injury after ICH is caused by local pressure, the so-called mass effect, and mechanical disruption of normal anatomy.[98] During the following hours and days secondary neuronal damage develops, caused mainly by the cytotoxicity of blood, excitotoxicity from glutamate that is released from the damaged neurons, oxidative stress, inflammation, and brain oedema.[2,51,99,100] Red blood cells start to degenerate and release haemoglobin (Hb) into the brain tissue and CSF, which is then further degraded to iron and haem.[98] Haemoglobin and its degradation products are highly cytotoxic and prone to cause oxidative damage.[101] Multiple cellular systems take part in the transport, detoxification and degradation these molecules, such as haptoglobin, a Hb-binding plasma protein produced in both the liver and oligodendrocytes[102], CD163-positive macrophages that scavenge Hb[103,104], and haem oxygenase-rich microglia that remove Hb and haem from the brain extracellular space.[100]

Intracerebral haemorrhage may also cause hydrocephalus. It is thought to arise partly from mechanical obstruction of the CSF flow, either by extraventricular compression or by intraventricular haemorrhage, and partly from the biological effects of the blood in the CSF.[105] The mechanical obstruction may happen at the level of interventricular foramina (foramina of Monro), cerebral aqueduct, 4th ventricle outlets (foramina of Luschka and Magendie) in the posterior fossa, or arachnoid villi.[106] Formation of fibrosis has been observed at the level of both 4th ventricle outlets and arachnoid villi.[106,107]

Haemoglobin degradation products, mainly iron, cause damage not only to the neurons but also to other types of brain cells. Iron and ferritin have been shown to accumulate in the periventricular areas and hippocampi in rats after intraventricular blood

injection and cause ependymal cell damage and death of ependymal cilia.[108-111] IVH has been demonstrated to damage ependymal cell layer in the choroid plexus and cause disruption of the blood brain barrier.[112] In addition, thrombin and activation of the coagulation cascade has been shown to be an individual causative factor in the formation of hydrocephalus after IVH.[113]

Hydrocephalus usually causes ventricular dilatation, which leads to ependymal cell damage in the choroid plexus and ventricular walls;[105,112] periventricular gliosis; a decrease in the periventricular and, more generally, cerebral blood flow;[114] an increase in the periventricular extracellular space and water content in the cortical grey matter;[115] and thinning of the white matter tracts and corpus callosum.[116]

Acute hydrocephalus related to ICH usually develops during the following hours or days after the ictus.[18] It usually causes decline in the level of consciousness, headache, nausea, and may eventually lead to death if left untreated.[117] If hydrocephalus develops more slowly, it can cause gait disturbance, urinary incontinence, and dementia, resembling idiopathic normal pressure hydrocephalus.[118]

2.2 Neurosurgical treatment of patients with ICH

Since the 1960s, surgical treatment of ICH has been considered controversial, especially in comatose patients.[10] In 1989, a randomised controlled study was performed at our hospital on surgical treatment of deep ICH. The study showed that the surviving patients were left in a very poor condition.[11] The subject has since been investigated extensively.

In a large-scale, multicentre, randomised controlled trial (RCT), STICH[13], Mendelow and co-workers randomised 1033 patients from 27 countries with a supratentorial ICH to initial conservative management (530 patients) or early surgery (503 patients), in which the operation was carried out within 24 hours of randomisation. Patients in the conservative group were able to cross over to the surgery group, and eventually, nearly one-quarter of the patients in the conservative treatment arm underwent surgery. Patients' median age was 62 years, and median haematoma volume was 38 ml. Only 24% of patients in the surgical group and 26% of patients in the medical treatment group had a favourable outcome, the difference being statistically insignificant. In addition, mortality did not differ between the groups. In subgroup analyses, those patients with a lobar haemorrhage located 1 cm or less from the surface showed some benefit from surgery.

After conducting a meta-analysis of all available RCTs on surgical treatment of spontaneous supratentorial ICH[119], the authors then designed another international multicentre RCT, STICH II[14], to evaluate the aforementioned subgroup from the original STICH trial. The STICH II trial recruited 601 conscious patients with a superficial, supratentorial, lobar ICH with a volume of 10 to 100 ml and without IVH. The patients were again randomised to receive early surgery (less than 12 hours from randomisation) or initial conservative management. Again, 21% of the patients in the conservative treatment group crossed over to the surgical treatment group. The results did not attain statistical significance; 62% of the patients in the initial conservative treatment group and 59% of the patients in the early surgery group had a poor functional outcome at 6 months.

It has been suggested that by using a traditional craniotomy approach, the surgeon-induced trauma to the surrounding tissues could eventually negate the positive effects of haematoma evacuation.[120] In response, mini-invasive techniques, such as endoscope-assisted aspiration and stereotactic aspiration have been studied.[121]

In a phase II randomised, international, multicentre trial, the MISTIE II trial, 96 patients were randomised to receive either best

medical treatment (40 patients) or mini-invasive catheter placement to the haematoma cavity, subsequent haematoma aspiration and clot irrigation with rTPA (56 patients).[122] The outcome did not differ between the groups, but the results proved that this was a viable approach. However, there was a higher rate of asymptomatic rebleeding in the surgical group. In further analyses of the MISTIE II data, mini-invasive surgery was associated with a decrease in perihaematomal oedema.[123] In the ongoing phase III MISTIE III trial, interim analyses revealed that the haematoma evacuation rate was up to 74%, and only 14% of the catheters required repositioning before administration of the rTPA.[124] The final results of the MISTIE III trial have not yet been published.

In addition to pharmacological clot removal, mini-invasive mechanical clot removal has also been used. Some studies have used endoscopic haematoma aspiration for evacuation of ICH or IVH. Already in 1989, a RCT on endoscopic haematoma evacuation versus best medical treatment showed better survival in the surgical treatment group, although the functional outcome was similar between the groups.[125] In 2016, MISTIE-ICES, a small subarm study of the MISTIE trial, concentrated on CT-guided endoscopic aspiration of supratentorial ICH.[126] Patients with an ICH of over 20 ml were randomised 3:1 to receive either best medical treatment or endoscopic ICH aspiration. The study showed that the technique was safe, resulted in removal of over two-thirds of the haematoma, and patients treated with endoscopic haematoma evacuation had a 12% greater likelihood of good outcome at one year.

Numerous surgical tools have been developed to assist in mini-invasive removal of ICH. Using a navigated, rather large (diameter 13.5 mm) tubular sheath (BrainPath endoport system, NICO, Indianapolis, IN, USA) to access the ICH cavity has been suggested.[127] In addition, in the ongoing INVEST trial, image-guided mini-invasive haematoma aspiration using a novel device combining irrigation, suction and vibration (Apollo System, Penumbra Inc, Alameda, CA, USA) is compared with best medical treatment.[128] In another initial safety study, ICH was evacuated using a catheter designed for intra-arterial thrombolysis inserted via a burr hole, combined with rTPA delivered into the haematoma cavity.[129]

Decompressive craniectomy for supratentorial ICH has also been suggested.[130] In a small single-centre RCT, 40 patients divided into two groups were randomised to receive standard microsurgical haematoma evacuation or a medium-size decompressive craniectomy (DC) and duraplasty combined with the standard haematoma evacuation. DC was associated with better survival, especially in young patients.[131] In a recent case-control study, 54 patients undergoing DC and haematoma evacuation were retrospectively compared with 72 patients who had received best medical treatment. The surgical treatment was associated with increased survival, but no significant difference emerged in functional outcome between the groups.[132] DC has been shown to be associated with increased perihaematomal oedema, although the mass effect was ameliorated by the surgical decompression.[133] A large multicentre RCT on DC versus best medical treatment in patients with a spontaneous deep ICH (SWITCH) is currently recruiting patients (https://clinicaltrials.gov/show/NCT02258919).

As the large RCTs on surgical treatment of spontaneous supratentorial ICH have shown surgical treatment not to be superior to best medical treatment, the rate of ICH evacuation has dropped and the rate of admissions to the Acute Stroke Units has risen, at least in the United Kingdom.[134] We concentrated on three subgroups of ICH patients still frequently referred to the neurosurgical service: patients with a cerebellar ICH, patients with ICH-related hydrocephalus, and young adults with ICH.

2.2.1 *Treatment of intracerebellar haemorrhage*

Intracerebral haemorrhage (ICH) in the cerebellum constitutes around 10% of all "spontaneous" non-traumatic, non-aneurysmal ICHs.[135] Before computerized tomography became widely available, cerebellar ICH was a silent killer – patients deteriorated rapidly and the diagnosis was often made post mortem.[136] In 1978, Little and co-workers showed in a case series of 10 subjects that patients with cerebellar ICHs over 3 cm in diameter benefited from surgical evacuation, while smaller ICHs could be treated medically.[137] Since then, there has been a wide consensus in the neurological and neurosurgical communities that cerebellar ICHs should be operated on, however, the scientific proof is mainly based on small retrospective series with conflicting results.[15]

Haemorrhage in the posterior fossa may cause brainstem compression and lead to impaired consciousness, respiratory failure, and lower cranial nerve dysfunction.[136] Compression or obstruction of the fourth ventricle may cause acute hydrocephalus.[19] To relieve brainstem compression and hydrocephalus, surgeons tend to favour posterior fossa craniectomy or craniotomy with haematoma evacuation in patients with a declining level of consciousness.[16] Some regard this as counter-intuitive, as the results for long-term outcome after surgery of cerebellar ICH are generally pessimistic.[17]

The recommendations for operative treatment vary in the literature. Numerous different criteria have been suggested for surgical evacuation or decompression: haematoma diameter > 3 cm[137], patients with brainstem compression[138,139], patients with GCS 4-13 and haematoma diameter > 40 mm[140], patients with a deteriorating level of consciousness and haematoma volume > 10 cm3[141], and even all patients with a cerebellar ICH.[142] In contrast, some authors do not recommend surgical treatment at all because of poor long-term results.[143] Clinicians usually tend to wait until clinical deterioration, and then proceed to operative treatment, especially in patients under the age of 70.[16]

The current treatment guidelines have contrasting recommendations regarding treatment of cerebellar ICH. European Stroke Organisation (ESO) treatment guidelines did not find strong evidence for when, how, or on whom surgical evacuation or decompression should be performed.[8] American Heart Association (AHA) guidelines recommend evacuation of cerebellar ICH in patients declining neurologically or suffering from brainstem compression and/or acute hydrocephalus.[7]

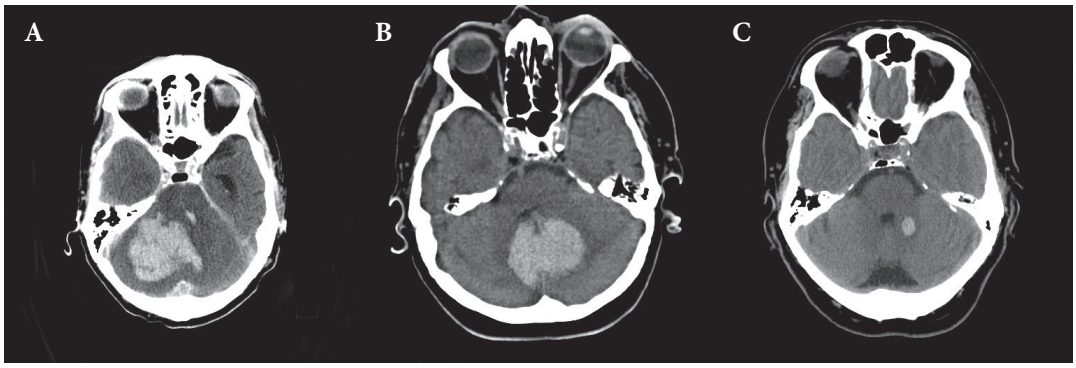


Figure 3. Three locations of cerebellar ICH in axial brain CT. (A) A large, lateral hemispheric cerebellar ICH causing hydrocephalus and brainstem compression. (B) A vermian cerebellar ICH that compresses the fourth ventricle but does not obliterate it. (C) A small, medial hemispheric cerebellar ICH that does not have any mass effect.

2.2.2 Treatment of ICH-related hydrocephalus

Acute hydrocephalus after ICH or IVH has been found to be a strong and independent predictor of poor functional outcome and mortality.[18] Traditionally, acute hydrocephalus has been considered an indication for surgery in patients with a cerebellar ICH.[19] while strong evidence to support treatment of hydrocephalus in other types of ICH is virtually absent.[20] The importance of hydrocephalus as an independent outcome-modifying factor after ICH was first published as late as 1998.[144] The authors did not note any differences in mortality after EVD insertion, and the finding was later reproduced in a small case series.[145] Although some encouraging results have been published[146], the majority of authors have found ICH-associated hydrocephalus to be a state of very high morbidity and it has been widely considered a sign of poor outcome.[20,147]

Regular treatment options for hydrocephalus are insertion of an EVD, sometimes combined with intraventricular fibrinolysis in patients with IVH, endoscopic third ventriculostomy, lumbar drainage, and insertion of a ventriculoperitoneal or ventriculoatrial shunt.[148] There have also been experimental reports on endoscopic third ventriculostomy for treatment of ICH-related hydrocephalus, especially combined with endoscope-assisted evacuation of IVH.[149]

Intraventricular fibrinolysis has been studied on hydrocephalic patients with IVH, where placing an EVD reduced mortality and increased rates of good functional outcome.[150] In a recently published large, double-blinded randomised trial of intraventricular alteplase versus saline, the patients who received alteplase had significantly lower 180-day case fatality, but higher rates of poor functional outcome.[151] In another study on intraventricular fibrinolysis, aggressive treatment with EVD and lumbar drainage significantly reduced shunt-dependency compared with an EVD alone.[152] However, no randomised studies on the treatment of ICH-related hydrocephalus have been published and there are no good criteria for when to place or remove an EVD.[20]

No randomised controlled trials exist on EVD placement for ICH-related hydrocephalus, and the literature is overall quite scarce.[20] However, it has been suggested that EVD insertion in patients with IVH was associated with good outcome (modified Rankin scale 0-3) at discharge.[150] In addition, multiple studies on the safety and efficacy of intraventricular fibrinolysis for treatment of IVH have been conducted in recent years. Using the recombinant tissue plasminogen activator (rTPA) alteplase, an intraventricular injection of one milligram every 8 hours via an EVD had the best efficacy and the lowest risk profile.[153,154] It has also been shown that adding a lumbar drain after the third and fourth ventricles were cleared from blood was safe and significantly reduced the rates of permanent shunt-dependent hydrocephalus compared with patients with conventional EVD and intraventricular fibrinolysis.[152,155]

In a recent double-blinded randomised trial of intraventricular alteplase versus saline, the patients who received alteplase had significantly lower 6-month mortality, but higher rates of poor functional outcome.[151] In the trial, all patients had an acute hydrocephalus and had received an EVD, after which the randomisation was performed. The authors drew the conclusion that routine intraventricular fibrinolytic treatment cannot be recommended in patients with IVH. It is, however, notable that the 6-month mortality in both groups was lower than that usually reported in studies of ICH-related hydrocephalus, 18% in the alteplase group and 29% in the saline group. The previously reported mortality rates of hydrocephalic ICH patients have varied between 55% (30-day mortality)[147] and 71% (in-hospital mortality).[145] One explanation for this difference may be that the patients were treated in a rather intensive fashion com-

pared with the more conservative treatment accorded to the average ICH patient.

In previous studies, factors associated with shunt-dependent hydrocephalus have been thalamic ICH location, persistent high intracranial pressure (ICP), lower arrival GCS, and longer duration of external drainage. The shunting rate has varied between 20% and 29%.[156,157] In a recent review, the authors suspected that 30-60% of patients needing an EVD would later need a shunt.[154] The current guidelines are somewhat encouraging regarding treatment of ICH-related hydrocephalus. The ESO guidelines do not give any strong recommendations about how, when, and for whom to place an EVD in the absence of RCTs. They do state, however, that it seems reasonable to apply an EVD in cases of clinical or radiological signs of hydrocephalus based on small, non-randomized studies.[8] The AHA guideline considers an EVD reasonable, especially in patients with a decreased level of consciousness.[7]

2.2.3 ICH in the young

Young ICH patients are an important subgroup. In young adults, aetiology of ICH is often different than in the elderly.[158] In addition, stroke affects not only the patients but their families as well, causing long-standing socio-economic consequences.[159] However, young age has been identified a positive prognostic factor for better survival after ICH.[9] As the incidence is higher in older age groups[1], most of the research is concentrated on the general population and therefore older age groups.

Contrary to the ICH incidence in the total population, it has decreased up to 47% in young adults in the United States between 1989 and 2009, accounting for 34% of stroke-related deaths.[160] Hypertension[158,161], smoking[58,161], hypocholesterolaemia, and excessive alcohol consumption are risk factors associated with ICH in the young.[158]

High numbers of patients with a structural aetiology have been observed,[158,161,162] although in some studies hypertensive ICHs have also been prevalent.[163,164] Short-term mortality has varied between 8% and 34%[158,165], while long-term mortality in the surviving patients was 11.2% in a 10-year follow-up.[166] A total all-cause mortality of 31.4% after a 20-year follow-up has been reported.[167]

2.3 Prognostic factors and ICH

Patients with ICH have very high mortality rates, overall mortality and morbidity being higher than in ischaemic stroke.[168,169] In current clinical practice, the prognosis is often based on the treating physician's experience and assumptions.[170] Overestimating the risk of death may lead to unnecessary withdrawal or limitation of treatment, while underestimating the risk of permanent unconsciousness or total dependence may lead to prolonged, futile treatment. Although the determination of "futile treatment" is complex, not least ethically, most clinicians consider that if the probability of survival was be around 5%, further treatment would be unethical and they would not recommend its continuation.[171]

Some attempts to predict the probability of death after an ICH had already been made in the last decades of 20th century[172-174], but since the publication of the ICH score by Hemphill et al. in 2001[9], numerous different scores have abounded in the neurological literature. To our knowledge, none are in current, widespread clinical use, with the possible exception of the original ICH score, although the most recent ASA treatment guidelines support the use of prognostic scores.[7]

Prognosis research has become more popular during the last 25 years, with nearly 100 000 publications in 2015 (Figure 4). This is not surprising, as it is a central concept in clinical medicine, referring to the 'risk of future health outcomes in people with a given disease or

condition'.[175] The PROGnosis RESearch Strategy (PROGRESS) partnership, a UK-based and Medical Research Council (MRC) -funded, international, interdisciplinary collaboration, was founded to improve the quality of research related to prognosis. They have identified four separate, but related research themes for prognosis research.

1. Fundamental prognosis research[175] should concentrate on defining the state and outcome of current care, e.g. outcome after the rupture and subsequent treatment of a cerebral AVMs[80], or the natural course ("natural history") of the disease, e.g. risk of rupture of untreated cerebral artery aneurysms.[176] It is important for planning of future trials and health care policies (in defining the need for preventive measures), for understanding the absolute treatment effects of said diseases compared with the general population, and as a framework for researching clinical outcomes.

2. Research on prognostic factors[177], which they define as 'any measure that, among people with a given startpoint (such as diagnosis of disease), is associated with a subsequent endpoint (such as death)', concentrates on finding different factors that divide patients into groups with a different risk of, for example, death. Different biomarkers often serve as prognostic factors, such as the presence of untreated hypertension as a risk factor for ICH[50], or the association of IVH with mortality after ICH.[178] Prognostic factors help in defining the severity of the disease and planning treatment algorithms for different subgroups, e.g. in low-grade glioma, where mutations in IDH1 gene and 1p19q co-deletions affect the outcomes and treatment decisions are now based on these factors.[179,180] Once a prognostic factor has been identified, it should be tested in different populations by, for instance, a meta-analysis.

3. Prognostic model research[181] deals with risk calculators and scores. A prognostic model is defined as '- - a formal combination of multiple predictors from which

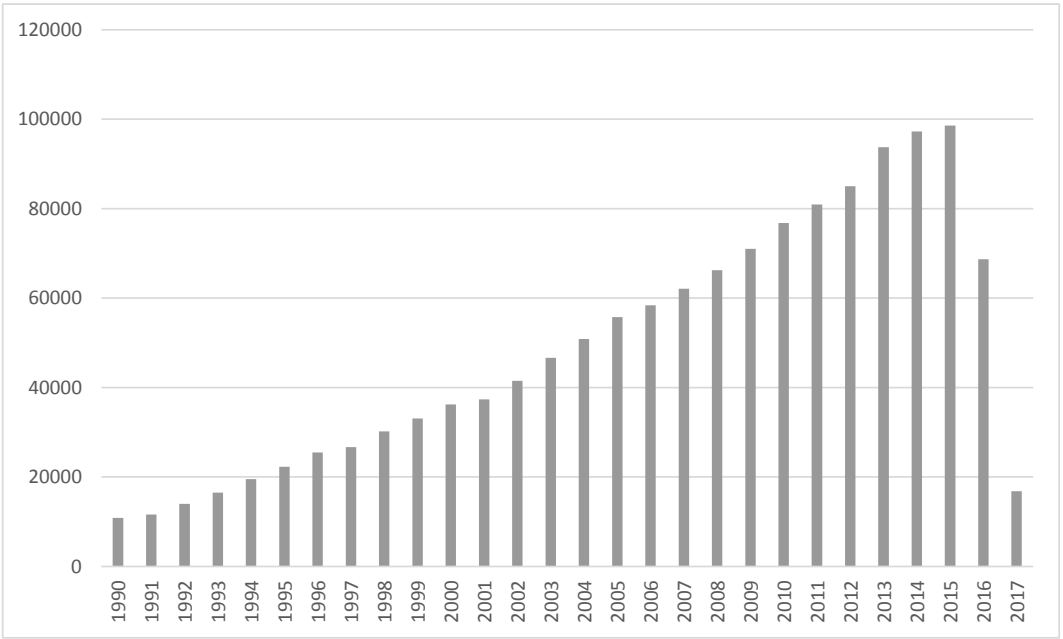


Figure 4. Annual number of publications in PubMed with the search term "prognosis" (5/2017).

risks of a specific endpoint can be calculated for individual patients'. Research on prognostic models may concentrate on developing prognostic models, validating these in external cohorts, or assessing the clinical importance of said models. A good example is the ICH score[9], a prognostic score developed for assessing mortality after ICH. The authors state that good prognostic models should be developed with a large data, be based on a prospective study plan with pre-selected prognostic factors, and be validated in external patient cohorts.

4. Stratified medicine research[182], where the objective is on finding different subgroups (strata) that benefit from certain treatment. It is defined as 'targeting of treatments - - according to the biological or risk characteristics shared by subgroups of patients'. In cancer research and treatment this is becoming more and more ordinary, e.g. in different subtypes of paediatric medulloblastoma, where treatment is tailored based on the results of genomic sequencing[183]. Such stratification is often the end product of prospective, randomised studies concentrated on finding therapies for these subgroups.

However, prognosis research is often seen as riddled with problems, e.g. using small, retrospective cohorts without a pre-specified statistical analysis plan[181], selection of outcomes or prognostic factors that produce the "most significant" p-values[182], publication bias in favour of small studies with positive results[184], and lack of external validation of prognostic models[185]. This has led to development of the TRIPOD ("Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis") checklist, a reporting guideline for studies on prognostic models that concentrates on avoiding these issues[186].

Different prognostic factors for mortality after ICH have been suggested. The ICH score[9] includes the following variables (as do numerous later models): age, ICH volume, GCS, infratentorial location, and the presence of IVH Other suggested prognostic factors are National Institutes of Health Stroke Scale score (NIHSS) [168,187,188], comorbidities[168,189-191], hyper- or hypotension[187,190,192], out-of-hours arrival[168], hyperglycaemia or diabetes[190,191,193], dialysis[190], cognitive decline[194], fever[187], low pulse pressure[187], subarachnoid blood[187], male gender[168], atrial fibrillation[168], coronary heart disease or peripheral artery disease[168], absence of dyslipidaemia[168], and the absence of previous stroke.[168] Hydrocephalus has also been identified as a strong prognostic factor for mortality after ICH, although it has not been included in prognostic scores.[144]

3 AIMS OF THE STUDY

The series of studies concentrated on evaluation of prognostic scores for ICH and on neurosurgical treatment of ICH in the patient subgroups a neurosurgeon meets most often: young patients, hydrocephalic patients, and patients with a cerebellar ICH. The following questions were addressed:

1. What is the best tool for mortality prognostication among the existing prognostic scores for ICH?

2. How does medical or surgical treatment modify the outcome of patients with an intracerebellar haemorrhage?

3. Does surgical treatment of patients with ICH-related hydrocephalus affect their mortality?

4. What is the outcome of young adults with ICH, and does surgical treatment affect their short- or long-term mortality?

4 PATIENTS AND METHODS

All of the studies (I-IV) were observational by nature and based on retrospective data collected at the Departments of Neurology and Neurosurgery at Helsinki University Hospital. The hospital is a tertiary-level university teaching hospital, with a catchment population of 1.8 million, which will increase to 2 million in 2018 as the Päijät-Häme province joins the tertiary district. However, most of the ICH patients come from the Uusimaa province with a population of 1.56 million, as the more distant secondary hospitals in Kotka and Lappeenranta have acute stroke units for conservative management of stroke patients. Helsinki University Hospital has the only neurological and neurosurgical emergency rooms on a 24/7 basis, and it is a national referral centre for cerebrovascular neurosurgery. All data were collected retrospectively from charts, electronic patient records, and imaging archives. Mortality data were derived from Statistics Finland's National Death Registry. The Helsinki University Hospital administration approved the study as a registry study with no patient contact or consent. Patients were treated according to ESO guidelines.[8] All deaths were included regardless of the cause. A two-sided $p < 0.05$ was considered significant for all analyses.

4.1 Publication I

4.1.1 Patients

For publication I, we used data from the Helsinki ICH study with 1013 consecutive patients admitted to the neurological emergency department of our hospital between January 2005 and March 2010.[3]

The patients were identified by the *International Classification of Diseases, 10th version* (ICD-10) code I61 during their stay in the acute phase or later during follow-up visits. Diagnosis data were retrieved from the electronic hospital discharge registry. All patient charts were retrieved. Patients with a traumatic haemorrhage, spontaneous epidural or subdural haemorrhage, or bleeding due to co-localised tumour (n=18) were excluded as non-strokes. Primary subarachnoid haemorrhage and haemorrhagic transformation of cerebral infarction (n=179) were excluded as well.

4.1.2 Prognostic scores

A thorough search was performed in PubMed, OvidSP, Web of Science, and Google to include all available prognostic models for ICH published after 1990. We used the search terms 'ICH', 'prognosis', 'score', 'scale', and 'validation'. None of the scores were used for clinical prognostication at our institute.

We calculated all scores for each included patient. The FUNC score[194] was derived to estimate good outcome instead of mortality, hence we used its reciprocal for the receiver operator curve (ROC) analyses. To determine the ICH volume, we preferred the same method as the original articles. The Graeb[195] and Hallevi[196] IVH scores were determined. The Tuhrim equation[174] included the IVH volume (cm^3) estimated by computer-based image analysis. As this was not available at our centre, we used the mathematical method by Hallevi.[196] Due to unavailability of some computerized volumetric methods and structured questionnaires at our institute, we used the best possible alternatives.

4.1.3 Statistical methods

The accuracy of the scores was evaluated for three different measures; 3-month all-cause mortality was chosen as the primary outcome, whereas in-hospital and 12-month mortality were measured as secondary outcomes.

We analysed the univariate associations of all the different score components and outcome. The ordinal and continuous score

components were tested for normality. The Kruskal-Wallis and Mann-Whitney U tests were used for skewed, and Analysis of Variance (ANOVA) for normally distributed data. Because of the time series nature of the analysis, we used Kaplan-Meier survival analysis with time from ICH to death up to 12 months as a continuous variable for the dichotomous score components. The Breslow-Wilcoxon test was used to evaluate univariate differences.

To estimate the best possible prognostic performance of all the score variables in a tailored logistic regression model, we divided the study population into derivation and validation cohorts stratified for age and ICH volume. After stratification by age and ICH volume, every other patient was classified in the derivation and every other patient in the validation cohort. The cohorts were tested for statistically significant differences. With all the score components forced to enter the model, a logistic regression model was constructed from the derivation cohort. We did not perform any dichotomization on either the continuous or the ordinal variables. The resulting model was tested on the validation cohort.

We calculated the areas under the curve (AUC) for the receiver operating curves (ROC) for all individual score components and for all different prognostic scores. The AUCs of a) the best-performing individual score component, b) the best-performing score, c) the original ICH score, d) GCS, and e) our optimized logistic regression model were tested against each other. The Youden index (J) was calculated to determine the optimal cut-off points and, further, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the selected scores. In addition, we created a bivariate correlation matrix and used Spearman's ρ and tolerance as analyses of collinearity to measure the relative independence of the different score components. In addition, to test for the goodness of fit in the prognostic models, Hosmer-Lemeshow test was used (results not shown).

The analyses were conducted using SPSS 20 (IBM Corp., Armonk, NY, USA). For the statistical differences in the AUCs, we used Z derived from ROC-kit v.1.0.3 software[197] (http://metz-roc.uchicago.edu/) with non-parametric assumptions and a U-statistic based method.[198]

4.2 Publications II and III

4.2.1 Patients

For these two publications, we augmented the data from publication I with additional data from the neurosurgical department. Patients between January 2005 and March 2010 with ICD-10 codes I60.8, I61, I67.4, I67.4, I67.5, I67.6, I67.7, I67.8, I67.9, I68, I69, Q28.1, Q28.2, and Q28.3 were screened to find all patients with a spontaneous, non-traumatic, non-aneurysmal ICH.

4.2.2 Imaging studies

Immediately on arrival, all patients underwent a computerised tomography (CT) and if needed, a CT angiography to exclude aneurysms, AVMs, and dural fistulae. If a tumour was suspected, MRI was performed. A neuroradiologist reviewed the imaging data. Patients with a macrovascular or structural cause for the haemorrhage (AVM, dural fistula, cavernous angioma, or tumour) were then excluded from the study. We assessed the haematoma location, maximal diameter, and volume. ICH volume was calculated using the ABC/2 method.[199]

4.2.3 Surgical treatment

As there are no decisive guidelines on the surgical treatment of ICH, indications for surgery were not guideline- or protocol-based. Neurosurgical treatment was individually considered in those patients who presented with a large ICH, declining level of consciousness, obstructive hydrocephalus, or imminent herniation, and were still considered salvageable. ICH evacuation was carried out using stand-

ard microneurosurgical techniques through a small open craniotomy (or craniectomy in the posterior fossa) under a high-magnification surgical microscope. We did not use mini-invasive or other experimental techniques.

Those patients with an intracerebellar haemorrhage receiving surgical treatment underwent a suboccipital paramedian or midline craniotomy and the haematoma was evacuated in a standard microneurosurgical manner. One patient underwent a primary bilateral decompressive craniectomy of the posterior fossa and subsequent haematoma evacuation.

If symptomatic hydrocephalus was present, patients received an external ventricular drain (EVD). EVD was placed at Kocher's point, preferably on the right side. No prophylactic antibiotics were used. EVD changes, duration of drainage, shunts, and shunt-related complications were recorded.

In publication II, EVD insertion was not considered surgical treatment in patients with an intracerebellar haemorrhage, as the mass effect caused by the haemorrhage in the posterior fossa was considered the real culprit. On the other hand, in publication III, both EVD or shunt insertion and cerebellar ICH evacuation were considered surgical treatment for ICH-related hydrocephalus, where releasing the intracranial pressure is usually enough.

4.2.4 *Treatment of unconscious patients and intensive care*

Level of consciousness on arrival was recorded on the Glasgow Coma Scale (GCS). The GCS verbal score for intubated patients was derived using the method of Meredith.[200] Unconscious patients were intubated and mechanically ventilated. Propofol was used for sedation of intubated patients. Systolic blood pressure (BP) was kept under 160 mmHg and controlled with labetalol or clonidine. Electrolyte levels and blood gases were routinely analysed. In case of paralysis of the lower cranial nerves and dysphagia, patients received a percutaneous tracheostomy bedside at the ICU. Length of ICU and stroke unit treatment were recorded.

4.2.5 *Characteristics and effect of surgical treatment on mortality*

We first compared the demographic and radiological differences and the differences in treatment between the patients who underwent haematoma evacuation and those who were treated conservatively in the whole dataset. To assess the effect of known outcome modifiers on long-term mortality, we used a Cox proportional hazards model after checking that the non-informative censoring assumption and the proportionality of the hazards assumption were met. Log-minus-log method was used to assess the proportionality assumption.

4.2.6 *Intracerebellar haemorrhage*

In publication II, based on how they had been treated, we divided the patients with a cerebellar ICH into a conservative or surgical treatment group for the analyses. The indications for surgery were determined case-by-case, weighing the haematoma size, declining level of consciousness, age, and possible comorbidities. Deeply unconscious patients with signs of midbrain or brainstem dysfunction, very high age, or severe comorbidities were treated medically. All operated patients underwent a postoperative computerized tomography (CT) scan on the first postoperative day to confirm that brainstem compression and hydrocephalus had relieved. Reoperations were recorded.

For the cerebellar ICHs, in addition to the other radiological variables, we assessed the vascular territory of the haematoma. We used a three-grade scale by Taneda to classify quadrigeminal cistern obliteration.[201] A three-grade scale by Kirollos was used to classify fourth ventricle compression.[202] Effacement of the

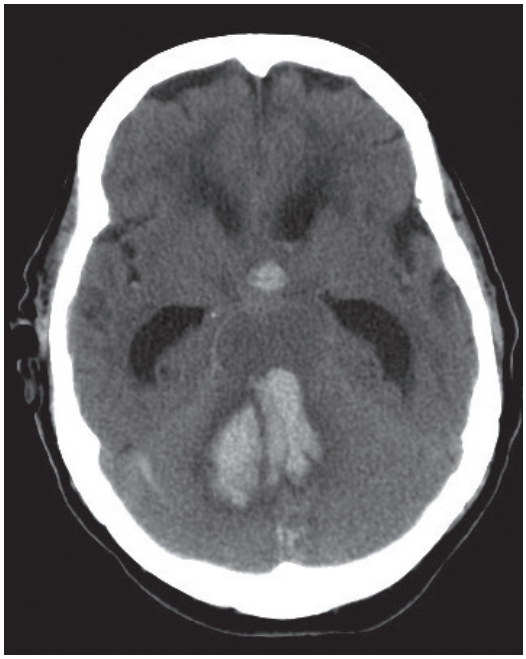


Figure 5. Example of a 'tight posterior fossa' as a sign of brainstem compression in an axial brain CT.

posterior fossa basal cisterns and obstructive hydrocephalus are criteria for 'tight posterior fossa', which was used as an indirect marker of brainstem compression (Figure 5).[139]

4.2.7 Hydrocephalus

We used the Stein classification for hydrocephalus.[203] They defined absence of hydrocephalus as a normal ratio of inner and outer cerebrospinal fluid (CSF) spaces without widening of the temporal horns in the absence of significant brain atrophy. 'Beginning' hydrocephalus (Figure 6A) was defined as abnormal ratio of inner and outer CSF spaces, with non-atrophic enlargement of at least one temporal horn. 'Moderate' hydrocephalus (Figure 6B) was defined as non-atrophic enlargement of one temporal and one frontal horn and sulcal effacement in at least one lobar region (frontal, temporal, parietal, or occipital). The definition for 'severe' hydrocephalus (Figure 6C) included the criteria for moderate hydrocephalus, in addition to sulcal effacement in two regions or bilateral basal cistern compression. To record intraventricular haemorrhage severity, we used the Hallevi IVH score.[196]

4.2.8 Outcomes

In publication II, we compared the in-hospital mortality, functional outcome of the medically and surgically treated patients with an intracerebellar haemorrhage at hospital discharge, and the impact of the chosen treatment on long-term mortality. In addition, we

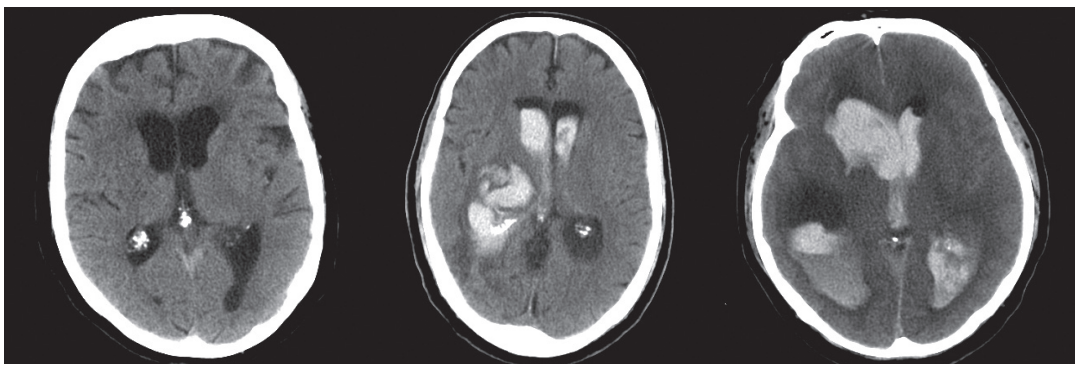


Figure 6. Stein classification of ICH-related hydrocephalus in an axial brain CT. A) 'Beginning', i.e. mild hydrocephalus. B) Moderate hydrocephalus. C) Severe hydrocephalus.

compared the demographics and radiological factors in the surgically and conservatively treated patients. We also constructed a binomial logistic regression model to assess the effect of different demographic and radiological factors on poor functional outcome or death at discharge (mRS 4-6).

In publication III, the primary outcome was 3-month mortality. We first compared the demographic, clinical, and radiological differences in hydrocephalic and non-hydrocephalic patients. Second, we examined only those patients who had at least 'beginning' hydrocephalus. We compared the patients who received surgical treatment for their hydrocephalus with those who did not to assess the effect of the treatment on mortality and to observe the differences in the baseline characteristics in these two groups. As a secondary outcome, we compared the 3-month mortality between two propensity score-matched groups of hydrocephalic patients: those who received surgical treatment for their hydrocephalus and those who did not. Surgical treatment was defined as 1) insertion of an EVD or a shunt, or 2) evacuation of an intracerebellar haemorrhage.

4.2.9 Statistical methods

SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The ordinal and continuous variables were tested for normality. We used the Kruskal-Wallis and Mann-Whitney U tests for skewed and one-way analysis of variance (ANOVA) for normally distributed data. Pearson's chi square was used to compare categorical variables between the groups.

In publication II, we used Kaplan-Meier analysis to assess the differences in long-term mortality. For univariate and multivariable regression, we used Firth penalised binomial regression to discard separation in the standard maximum likelihood analyses.

The propensity score matching and analysis were conducted using the PS Match 3.04 extension package for SPSS by Felix Thoemmes (http://arxiv.org/abs/1201.6385). For the comparison of surgically and conservatively treated patients in the whole dataset, we included age, GCS on arrival, and ICH location in the propensity model. We used nearest neighbour matching with a calliper of 0.2 standard deviation (SD) to find matching pairs.

For the surgically and conservatively treated patients with hydrocephalus in publication III, we included age, GCS on arrival, haematoma volume, hydrocephalus severity, and infratentorial haemorrhage in the propensity model. We used exact matching on infratentorial haemorrhage and hydrocephalus severity, while nearest neighbour matching with a calliper of 0.2 SD was used on the other variables.

4.3 Publication IV

4.3.1 Patients and treatment

Due to the low incidence in the young, we collected data from a longer time period: from January 2000 to March 2010. We used the same ICD-10 criteria as in publications II and III with one exception: the structural haemorrhages related to AVMs, dural fistulae, cavernous angiomas, and tumours were included in the study to characterise the entire spectrum of causes of ICH in young adults. Hypertensive microangiopathy was considered the cause of ICH if hypertension was present and the haemorrhage was deep or infratentorial. Structural causes were identified on brain imaging and surgical specimens. Other causes included cerebral venous thrombosis, vasculitis, illicit drug use, eclampsia, liver disease, and the syndrome of hemolysis, elevated liver enzymes, and low platelet count.

4.3.2 Statistical methods

The analyses were performed using SPSS 20 (IBM Corp., Armonk, NY, USA). We used Pearson's Chi square for categorical variables,

and Mann-Whitney U or Kruskal-Wallis tests for skewed continuous variables. Binomial logistic regression with the backward likelihood ratio method was used to find the independent predictors for 3-month mortality. In addition, we constructed a propensity score to compare the surgically and conservatively treated patients. We included the known outcome modifiers: age, sex, NIHSS score, location and volume of ICH, structural cause, intraventricular blood, hydrocephalus, radiological herniation, and multiple haemorrhages, in the propensity model.

5 RESULTS

5.1 ICH scores (Publication I)

In publication I, we discovered 19 different prognostic scores for ICH. The ICH Functional Outcome Score (ICH-FOS)[193] performed best with a small edge over NIHSS for 3- and 12-month mortality, and for in-hospital mortality they performed equally well.

5.1.1 Prognostic models

We found 19 different prognostic scores and models for ICH (Table 1). Many of the score shared similar point assignments, reflecting the original ICH score (Table 2A-C). Additionally, five scores provided a formula for the probability of death or survival (Table 3).[9] For this publication, we used data from the original Helsinki ICH study, collected from the neurological department at our institute between January 2005 and March 2010. Of the 1013 consecutive patients with a spontaneous ICH in the database, 131 were excluded due to missing data, leaving 882 patients for the analyses. The observed in-hospital mortality was 23.6%, 3-month mortality 31.0%, and 12-month mortality 35.3%.

Table 1. Included scores and their derivation cohorts, locations and primary outcomes.

Year	Score name	n	Prospective	Location (n of centres)	Mortality outcomes	Functional outcomes
1993	Cincinnati model[172]	162	No	OH, USA (20)	30-day	30-day OHS
1995	Masé equation[173]	138	No	Trieste, Italy (1)	30-day	-
1999	Tuhrim equation[174]	129	Yes	New York, NY, USA (1)	30-day	-
2001	ICH score (oICH)[9]	152	No	San Francisco, CA, USA (2)	30-day	-
2003	New ICH score (nICH) and modified ICH score (mICH)[187]	142	No	Hong Kong, China (1)	30-day	30-day mRS 0-2
2006	Modified ICH–A and –B (mICH-A and –B)[189]	153	Yes	Junin and Bahia Bianca, Argentina (2)	30-day	180-day GOS 4-5, 180-day GOS 2-3
2006	Essen ICH score[188]	340	No	Germany (30)	100-day	100-day BI 95-100, 100-day BI 0-90
2006	GP on Stage score (GPoS)[204]	995	Yes	Asia (14)	-	Discharge mRS 5-6
2007	ICH grading scale (ICH-GS)[205]	378	Yes	Guadalaraya, Mexico (1)	In-hospital, 30-day	30-day GOS 4-5
2008	FUNC score[194]	418	Yes	Boston, MA, USA (1)	-	90-day GOS 4-5
2008	Cho's MICH score[206]	226	Yes	Taichung, Taiwan (1)	180-day	180-day GOS 4-5, 180-day BI 55-100
2008	ICH outcome score (ICHOS)[192]	107	No	Taoyan, Taiwan (1)	30-day	-
2009	Simplified ICH score (sICH)[190]	293	No	Taichung, Taiwan (1)	30-day	-
2011	Landseed ICH score (LSICH)[191]	285	No	Taoyan, Taiwan (1)	In-hospital	Discharge BI < 40
2012	ICH index (ICHI)[149]	227	No	Chongqing, China (1)	In-hospital	-
2013	ICH Functional Outcome Score (ICH-FOS)[193]	1953	No	China (132)	-	1-year mRS 3-6
2013	Get with the guidelines (GWTG) Stroke score[168]	~6000	Yes	USA (1046)	In-hospital	-

Table 2A. Different prognostic scores and their point assignments. Many of the scores are based on the same format with slight differences in the point distribution.

	ICH score		mICH		mICH-A		mICH-B		Essen		ICH-GS			FUNC		Cho's MICH score		ICHOS		LSICH		ICH-FOS		
Age	< 80	**0**	<80	**0**	<50	**0**	<65	**0**	<60	**0**		<45	**1**	>=80	**0**			< 70	**0**				<=59	**0**
	≥ 80	**1**	>=80	**1**	50-64	**1**	>=65	**1**	60-69	**1**		45-64	**2**	70-79	**1**			≥ 70	**2**				60-69	**1**
					>=65	**2**			70-79	**2**		>=65	**3**	<70	**2**								70-79	**2**
									>=80	**3**													>=80	**4**
ICH Volume	<30 cm3	**0**	<30 cm3	**0**	<30 cm3	**0**	<30 cm3	**0**			*supra-tentorial*	*infra-tentorial*		>60 cm3	**0**	<=20 cm3	**0**			< 30 ml	**0**	*supra-tentorial*	*infra-tentorial*	
	>=30 cm3	**1**	>=30 cm3	**1**	30-50 cm3	**1**	30-50 cm3	**1**			<40 cm3	<10 cm3	**1**	30-60 cm3	**2**	21-50 cm3	**1**			≥ 30 ml	**1**	<40 cm3	<10 cm3	**0**
					>50 cm3	**2**	>50 cm3	**2**			40-70 cm3	10-20 cm3	**2**	<30 cm3	**4**	>=51 cm3	**2**					40-70 cm3	10-20 cm3	**2**
											>70 cm3	>20 cm3	**3**									>70 cm3	>20 cm3	**2**
GCS score	13-15	**0**			14-15	**0**	14-15	**0**				13-15	**1**	<=8	**0**	13-15	**0**	12-15	**0**	13-15	**0**		13-15	**0**
	5-12	**1**			9-13	**1**	9-13	**1**				9-12	**2**	>=9	**2**	5-12	**1**	9-11	**1**	5-12	**1**		9-12	**1**
	3-4	**2**			6-8	**2**	5-8	**2**				3-8	**3**			3-4	**2**	3-8	**4**	3-5	**2**		3-8	**2**
					3-5	**3**	3-4	**3**																
NIHSS			0-10	**0**					0-5	**0**													0-5	**0**
			11-20	**1**					6-10	**1**													6-10	**2**
			21-40	**2**					11-15	**2**													11-15	**3**
									16-20	**3**													16-20	**4**
									>20 or coma	**4**													>20	**5**
ICH location	supra-tentorial	**0**	supra-tentorial	**0**								supra-tentorial	**1**	infra-tentorial	**0**								supra-tentorial	**0**
	infra-tentorial	**1**	infra-tentorial	**1**								infra-tentorial	**2**	deep	**1**								infra-tentorial	**1**
														lobar	**2**									
IVH	no	**0**	no	**0**	no	**0**	no	**0**				no	**1**							no	**0**		no	**0**
	yes	**1**	yes	**1**	Graeb 1-4	**1**	Graeb <=3	**1**				yes	**2**							yes	**1**		yes	**1**
					Graeb 5-8	**2**	Graeb >3	**2**																
					Graeb >9	**3**																		
Others					***comorbidities***		***comorbidities***		***NIHSS alertness***					***Pre-ICH cognition***		***IVH or hydrocephalus***		***Systolic BP (mmHg)***		***Diabetes mellitus***			***Blood glucose***	
					no	**0**	no	**0**	alert	**0**				impaired	**0**	no	**0**	130 - 199	**0**	no	**0**		<=11.0 mmol/l	**0**
					yes	**1**	yes	**1**	drowsy	**1**				normal	**1**	yes	**1**	< 130 or ≥ 200	**1**	yes	**1**		>=11.1 mmol/l	**1**
									stupor	**2**														
									coma	**3**														
Total score		**0-6**		**0-6**		**0-13**		**0-9**		**0-10**			**5-13**		**0-11**		**0-5**		**0-7**		**0-5**			**0-16**

Table 2B. Some of the scores also included dialysis treatment, body temperature or blood glucose.

sICH		
GCS	14-15	**1**
	13-9	**2**
	5-8	**3**
	3-4	**4**
Age	< 80	**1**
	≥ 80	**2**
Hypertension	no	**1**
	yes	**2**
Blood glucose	≤ 11 mmo/l	**1**
	> 11 mmol/l	**2**
Dialysis	no	**1**
	yes	**2**
Total score		**5-12**

nICH		
NIHSS	0-10	**0**
	11-20	**1**
	21-40	**2**
Temperature	≤ 36 °C	**0**
	> 36 °C	**1**
Pulse pressure	≥ 60 mmHg	**0**
	< 60 mmHg	**1**
IVH	no	**0**
	yes	**1**
SAH	no	**0**
	yes	**1**
Total score		**0-6**

Table 2C. The GWTG-Stroke Risk Score was designed for all stroke types and it includes also variables that are not directly related to the patient, but may have impact on the treatment choices, i.e. mode and time of arrival.

GWTG-Stroke Risk Score		
NIHSS	0-2	**0**
	3-5	**9**
	6-10	**18**
	11-15	**30**
	16-20	**40**
	21-25	**47**
	>25	**56**
Age	<60	**0**
	60-70	**3**
	70-80	**6**
	>=80	**8**
Mode of arrival	Private transport	**0**
	Already in hospital	**8**
	Ambulance from scene	**9**
Gender	Female	**0**
	Male	**2**
AF present	no	**0**
	yes	**5**
History of stroke/TIA	yes	**0**
	no	**2**
Previous CHD	no	**0**
	yes	**4**
Peripheral vascular disease	no	**0**
	yes	**3**
History of dyslipidemia	yes	**0**
	no	**3**
Arrival 7am-5pm Mon to Fri	yes	**0**
	no	**1**
Stroke type	Uncertain	**0**
	Ischemic	**1**
	ICH	**18**
	SAH	**27**
Total score		**0-120**

Table 3. Five of the scores were based on a mathematical formula.

Score	**Formula**
Tuhrim equation for 30-day mortality[174]	p = e^z/(1+e^z) z = (-3.3125 + 0.018 * size of ICH in ml + 0.0979 * size of intraventricular haemorrhage (IVH) in ml + 0.5832 (if pulse pressure > 85mmHg) + 2.27859 (if GCS < 9) – 0.9567 (if hydrocephalus present)
ICHI index for in-hospital mortality[149]	p = age/10 + glucose in mmol/l + white blood cell count in 10*9/l – GCS
GWTG score for in-hospital mortality[168]	p = 1/(1 + exp(5.949803 - 0.066087*GWTG total score))
GPoS probability of mRS 5-6 at discharge[204]	p = e^z/(1+e^z) z = 2.7915 + 0.8637 (if temp ≥ 37.8°C) + 0.8992 (if ICH volume ≥ 30 ml) + 0.9294 (if IVH present) – 0.3653 * GCS
Masé model survival probability at 30 days[173]	p = 1/(1+e^0.5242 – 0.2521 * GCS + 1.7536 (if IVH present) + 0.0249 * VOL) VOL = 2.7 if ICH volume < 8.3cm^3, 11.4 if volume 8.3-20.4 cm^3, 28.8 if volume 20.5-47.7 cm^3 and 76.8 if volume > 47.7 cm^3

5.1.2 Association with mortality

The majority of the score components were associated with mortality in univariate analyses (Tables 4 and 5). Of the continuous variables, only "Systolic blood pressure", "Pulse pressure", and "Temperature" were not associated with mortality. Thus, nearly all of these factors had prognostic importance.

Table 4. Demographics of the study population: dichotomous score components and their association with mortality. Comorbidities were classified as presence of any major cardiovascular, renal, pulmonary, or metabolic conditions such as end-stage cancer, New York Heart Association (NYHA) class IV cardiac failure or coronary heart disease, dialysis-dependent renal insufficiency, hepatic cirrhosis, or immunodeficiency.

		In-hospital mortality, % (n)	3-month mortality, % (n)	12-month mortality, % (n)	p
Sex					0.019
	Male (n=508)	136 (26.8%)	171 (33.7%)	192 (37.8%)	
	Female (n=374)	72 (19.3%)	102 (27.3%)	119 (31.8%)	
Cortical location					0.510
	Yes (n=338)	76 (22.5%)	96 (28.4%)	115 (34.0%)	
	No (n=554)	132 (24.3%)	177 (32.5%)	196 (36.0%)	
Deep (including thalamic) location					0.1291
	Yes (n=483)	122 (25.3%)	164 (34.0%)	182 (37.7%)	
	No (n=399)	86 (21.6%)	109 (27.3%)	129 (32.3%)	
Infratentorial location					< 0.001
	Yes (n=123)	49 (39.8%)	55 (44.7%)	56 (45.5%)	
	No (n=759)	159 (20.9%)	218 (28.7%)	255 (33.6%)	
Intraventricular haemorrhage					< 0.001
	Yes (n=354)	143 (40.4%)	186 (52.5%)	198 (55.9%)	
	No (n=528)	65 (12.3%)	87 (16.5%)	113 (21.4%)	
Subarachnoid haemorrhage					0.076
	Yes (n=113)	46 (40.7%)	61 (54.5%)	69 (61.1%)	
	No (n=769)	162 (21.1%)	212 (27.6%)	242 (31.5%)	
Hydrocephalus					< 0.001
	Yes (n=123)	83 (67.5%)	95 (77.2%)	96 (78.0%)	
	No (n=759)	125 (16.5%)	178 (23.5%)	215 (28.3%)	
Dialysis					0.631
	Yes (n=14)	4 (28.6%)	5 (35.7%)	5 (35.7%)	
	No (n=868)	204 (23.5%)	268 (30.9%)	306 (35.3%)	
Comorbidities					< 0.001
	Yes (n=384)	102 (26.6%)	139 (36.2%)	162 (42.2%)	
	No (n=498)	106 (21.3%)	134 (26.9%)	149 (29.9%)	
Pre-ICH cognitive deficit					< 0.001
	Yes (n=40)	14 (35.0%)	21 (52.5%)	26 (65.0%)	
	No (n=842)	194 (23.0%)	252 (29.9%)	285 (33.8%)	
Atrial fibrillation					< 0.001
	Yes (n=90)	34 (37.8%)	40 (44.4%)	45 (50.0%)	
	No (n=792)	174 (22.0%)	233 (29.4%)	266 (33.6%)	
Previous stroke or TIA					0.103
	Yes (n=144)	38 (26.4%)	49 (34.0%)	59 (41.0%)	
	No (n=738)	170 (23.0%)	224 (30.4%)	252 (34.1%)	
Peripheral artery disease					0.032
	Yes (n=15)	7 (46.7%)	7 (46.7%)	8 (53.5%)	
	No (n=867)	201 (23.2%)	266 (30.7%)	303 (34.9%)	
Coronary heart disease					< 0.001
	Yes (n=122)	37 (30.3%)	54 (44.3%)	63 (51.6%)	
	No (n=760)	171 (22.5%)	219 (28.8%)	248 (32.6%)	
Dyslipidemia					0.292
	Yes (n=177)	33 (18.6%)	51 (28.8%)	57 (32.2%)	
	No (n=705)	175 (24.8%)	222 (31.5%)	254 (36.0%)	
After-hours arrival					0.638
	Yes (n=524)	121 (23.1%)	160 (30.5%)	182 (34.7%)	
	No (n=358)	87 (24.3%)	113 (31.6%)	129 (36.0%)	
Arrival by ambulance					< 0.001
	Yes (n=774)	200 (25.8%)	264 (34.1%)	301 (38.9%)	
	No (n=108)	8 (7.4%)	9 (8.3%)	10 (9.3%)	
Arrival by other than ER					0.911
	Yes (n=13)	4 (30.8%)	5 (38.5%)	5 (38.5%)	
	No (n=869)	204 (23.5%)	268 (30.8%)	306 (35.2%)	
Arrival by private transport					< 0.001
	Yes (n=95)	4 (4.2%)	4 (4.2%)	5 (5.3%)	
	No (n=787)	204 (25.9%)	269 (34.2%)	306 (38.9%)	
Diabetes					0.321
	Yes (n=125)	32 (25.6%)	41 (32.8%)	50 (40.0%)	
	No (n=757)	176 (23.2%)	232 (30.6%)	261 (34.5%)	

Table 5. Demographics of the study population: continuous score components and their prognostic performance.

Variable	**Median (IQR)**	**In-hospital mortality, AUC**	**3-month mortality, AUC**	**12-month mortality, AUC**
Age (years)	68 (58-78)	0.559 (0.515-0.604)	0.633 (0.593-0.674)	0.658 (0.620-0.696)
ICH volume (ml)	9.70 (3.76-26.1)	0.759 (0.720-0.799)	0.761 (0.726-0.797)	0.757 (0.723-0.791)
GCS	14 (11-15)	0.825 (0.790-0.860)	0.790 (0.755-0.824)	0.767 (0.732-0.801)
NIHSS	11 (4-19)	0.852 (0.821-0.882)	0.848 (0.820-0.876)	0.826 (0.797-0.855)
NIHSS alertness	0 (0-1)	0.813 (0.776-0.849)	0.778 (0.742-0.814)	0.753 (0.717-0.789)
Graeb score	0 (0-4)	0.733 (0.690-0.776)	0.743 (0.705-0.781)	0.717 (0.680-0.755)
Temperature (°C)	36.7 (36.3-37.2)	0.584 (0.534-0.633)	0.582 (0.539-0.626)	0.559 (0.516-0.601)
Blood glucose (mmol/l)	7.2 (6.1-9.1)	0.686 (0.646-0.726)	0.663 (0.625-0.701)	0.645 (0.608-0.683)
Systolic blood pressure (mmHg)	172 (149-193)	0.541 (0.493-0.590)	0.533 (0.490-0.576)	0.516 (0.476-0.557)
Pulse pressure (mmHg)	79 (63-96)	0.545 (0.496-0.593)	0.546 (0.502-0.589)	0.539 (0.497-0.580)

5.1.3 Prognostic performance

In the receiver operating curve (ROC) analyses of the individual score components, the National Institutes of Health Stroke Scale (NIHSS) had the highest area under curve (AUC) at every time point (Table 6). In the ROC analyses of the different scores, the ICH Functional Outcome Score (ICH-FOS)[193] performed best. The experimental regression model produced good AUC values for all time points (Table 7).

Table 6. Prognostic performance of the different scores.

Score name	**In-hospital mortality, AUC**	**3-month mortality, AUC**	**12-month mortality, AUC**
Cincinnati model[172]	0.7898 (0.754-0.825)	0.7664 (0.734-0.799)	0.7393 (0.708-0.771)
Masé equation[173]	0.8570 (0.827-0.888)	0.8480 (0.819-0.877)	0.8230 (0.793-0.853)
Tuhrim equation[174]	0.6580 (0.611-0.705)	0.6293 (0.587-0.672)	0.6187 (0.578-0.672)
ICH score (oICH [9]	0.8414 (0.811-0.872)	0.8454 (0.818-0.873)	0.8163 (0.787-0.846)
New ICH score (nICH)[187]	0.8497 (0.821-0.879)	0.8661 (0.841-0.891)	0.8453 (0.819-0.872)
Modified ICH Score (mICH)[187]	0.7931 (0.759-0.827)	0.8010 (0.770-0.832)	0.7881 (0.757-0.819)
Modified ICH–A (mICH-A)[189]	0.8498 (0.818-0.882)	0.8584 (0.831-0.886)	0.8392 (0.811-0.867)
Modified ICH-B (mICH-B)[189]	0.8500 (0.818-0.882)	0.8574 (0.830-0.885)	0.8381 (0.810-0.866)
Essen ICH score[188]	0.8387 (0.807-0.870)	0.8539 (0.826-0.882)	0.8470 (0.820-0.875)
GP on Stage score (GPoS)[204]	0.8520 (0.821-0.884)	0.8370 (0.808-0.867)	0.8100 (0.799-0.841)
ICH grading scale (ICH-GS)[205]	0.8429 (0.811-0.875)	0.8419 (0.814-0.870)	0.8156 (0.786-0.845)
FUNC score[194]	0.8086 (0.771-0.843)	0.8126 (0.781-0.845)	0.7858 (0.753-0.818)
Cho's MICH score[206]	0.8503 (0.820-0.880)	0.8395 (0.811-0.868)	0.8125 (0.783-0.842)
ICH outcome score (ICHOS)[192]	0.7570 (0.716-0.798)	0.765 (0.729-0.801)	0.7620 (0.728-0.796)
Simplified ICH score (sICH)[190]	0.7897 (0.754-0.826)	0.7781 (0.745-0.812)	0.7654 (0.733-0.798)
Landseed ICH score (LSICH)[191]	0.8280 (0.794-0.862)	0.8170 (0.785-0.849)	0.7890 (0.757-0.822)
ICH index (ICHI)[149]	0.7858 (0.751-0.821)	0.7688 (0.735-0.803)	0.7462 (0.712-0.780)
ICH Functional Outcome Score (ICH-FOS)[193]	0.8661 (0.838-0.896)	0.8802 (0.855-0.906)	0.8642 (0.838-0.891)
Get with the guidelines (GWTG) Stroke score[168]	0.8540 (0.824-0.883)	0.860 (0.833-0.887)	0.8450 (0.818-0.872)

Table 7. Performance of our tailored logistic regression model, with all different score components included.

	In-hospital mortality, AUC	3-month mortality, AUC	12-month mortality, AUC
Derivation cohort	0.9090 (0.875-0.944)	0.9030 (0.871-0.934)	0.8830 (0.849-0.917)
Validation cohort	0.8350 (0.792-0.879)	0.8660 (0.830-0.902)	0.8660 (0.830-0.901)
All patients	0.8730 (0.844-0.901)	0.8900 (0.867-0.913)	0.8740 (0.850-0.899)

5.1.4 Comparison of scores' performance

We then compared the AUC results of the best-performing single score component (NIHSS), the best-performing score (ICH-FOS), GCS, the original ICH score, and our regression model against each other. For in-hospital mortality, no significant differences emerged between NIHSS, GCS, or ICH-FOS scores. The original ICH score was equal to NIHSS and GCS, but inferior to the ICH-FOS score. For 3- and 12-month mortality, ICH-FOS was the best performer, with a statistically significant difference to the other tested scores, with a minor edge over NIHSS (Table 8). The optimal cut-off for ICH-FOS was 8 points for in-hospital and 3-month mortality, and 7 points for 12-month mortality. For NIHSS, the optimal cut-off for in-hospital mortality was 14 points.

Table 8. Statistical significance of the differences in prognostic performance at the three time points. The results for the regression model are presented for all patients.

	NIHSS	GCS	oICH [9]	ICH-FOS [193]
In-hospital mortality	p	p	p	p
GCS	0.3827	-	-	-
oICH	0.4858	0.5997	-	-
ICH-FOS	0.1522	0.1600	0.0092	-
Regression model (all patients)	0.1669	0.1037	0.0316	0.7058
3-month mortality				
GCS	0.0411	-	-	-
oICH	0.8786	0.0506	-	-
ICH-FOS	0.0003	0.0008	0.0002	-
Regression model (all patients)	0.0020	0.0003	<0.0001	0.6241
12-month mortality				
GCS	0.0366	-	-	-
oICH	0.4928	0.0854	-	-
ICH-FOS	<0.0001	0.0003	<0.0001	-
Regression model (all patients)	<0.0001	<0.0001	<0.0001	0.2588

5. 2 Characteristics and effect of surgical treatment on mortality (Publications II and III)

5.2.1 *Demographics and presentation*

The data used in publications II and III included 1075 patients with a non-traumatic, non-aneurysmal ICH between January 2005 and March 2010 presenting at the neurological and neurosurgical emergency rooms at our institute. Patients' mean age was 67.4 years, with a slight male predominance. A history of atrial fibrillation was found in 13.7% of patients, 62.3% had hypertension, and 13.3% were diabetic (Table 9). The mean haematoma volume was 25.5 ml, and the patients were in rather good condition, with a median GCS of 14. The majority of the haemorrhages were deep (basal ganglia or thalamic) ICHs (Table 10). All but three patients (99.7%) underwent a CT scan, CT angiography was performed in 295 patients (27.4%), MRI in 143 (13.3%), and DSA in 12 (1.1%) of the patients.

Table 9. Demographics of the conservatively and surgically treated patients and their differences.

	All patients (n=1075)	**Conservative treatment (n=967)**	**Surgical treatment (n=108)**	**p**
Age in years, mean (95% CI)	67.4 (66.6-68.2)	68.1 (67.3-69)	60.6 (58.3-62.9)	< 0.001
Male gender, n (%)	618 (57.5%)	562 (58.1%)	56 (51.9%)	0.212
Atrial fibrillation, n (%)	147 (13.7%)	138 (14.3%)	9 (8.3%)	0.088
Hypertension, n (%)	670 (62.3%)	621 (64.2%)	49 (45.4%)	< 0.001
Diabetes, n (%)	143 (13.3%)	136 (14.1%)	7 (6.5%)	0.028
Liver disease, n (%)	43 (4.0%)	38 (3.9%)	5 (4.6%)	0.725
Heavy drinking, n (%)	151 (14.0%)	135 (14.0%)	16 (14.8%)	0.809
Warfarin, n (%)	155 (14.4%)	143 (14.8%)	12 (11.1%)	0.302
Any antiplatelet drug, n (%)	266 (24.8%)	252 (26.1%)	14 (13.0%)	0.003
Statins, n (%)	195 (18.1%)	180 (18.7%)	15 (13.9%)	0.227
mRS at arrival, median (IQR)	0 (0), range 0-5	0 (0), range 0-5	0 (0), range 0-3	0.001

Table 10. Radiological and clinical differences in the conservatively and surgically treated patients.

	All patients (n=1075)	**Conservative treatment (n=967)**	**Surgical treatment (n=108)**	**p**
GCS at arrival, median (IQR)	14 (9-15)	14 (10-15)	12 (4-14)	< 0.001
Systolic BP at arrival, mean (95% CI)	174 (172-176)	173 (171-175)	180 (174-187)	0.052
Haematoma volume in ml, mean (95% CI)	25.5 (23.4-27.6)	22.3 (20.3-24.3)	52.0 (44.6-59.5)	< 0.001
Maximal diameter in mm, mean (95% CI)	41.8 (40.6-43.1)	39.9 (38.5-41.1)	57.6 (54.5-60.7)	< 0.001
Intraventricular blood, n (%)	476 (44.3%)	413 (42.7%)	63 (58.3%)	0.002
Location, n (%)				
Cortical (lobar)	324 (30.1%)	296 (30.6%)	28 (25.9%)	0.314
Deep	574 (53.4%)	533 (55.1%)	41 (38.0%)	0.001
Brainstem	64 (6.0%)	62 (6.4%)	2 (1.9%)	0.058
Cerebellum	104 (9.7%)	68 (7.0%)	36 (33.3%)	< 0.001
Intraventricular	9 (0.8%)	8 (0.8%)	1 (0.9%)	0.915
Hydrocephalus, n (%)				< 0.001
No	778 (72.4%)	734 (75.9%)	44 (40.7%)	
'Beginning'	104 (9.7%)	81 (8.4%)	23 (21.3%)	
'Moderate'	114 (10.6%)	89 (9.2%)	25 (23.1%)	
'Severe'	79 (7.4%)	63 (6.5%)	16 (14.8%)	

5.2.2 *Differences in surgically and conservatively treated patients*

The operated patients were younger and had less comorbidities such as hypertension and diabetes. No statistically significant differences were present in the use of warfarin, but the operated patients less often used antiplatelet drugs. Operated patients' premorbid functional status was statistically better (p=0.001), although the mean mRS in both groups was 0 with an interquartile range of 0 (Table 9). Operated patients had significantly lower GCS on arrival, and their haematoma volumes and maximal haematoma diameters were significantly larger as well. They had a greater incidence of intraventricular haemorrhage and hydrocephalus. In operated patients, the haemorrhages were less likely to be located in the deep (basal ganglia or thalamus) area (p=0.001) and more likely to be in the cerebellum (p < 0.001) (Table 10). For these analyses, we classified all haemorrhages extending to the brainstem as brainstem haemorrhages, and all haemorrhages extending to basal ganglia (but not to the brainstem) as basal ganglia haemorrhages due to the functional consequences of neuronal damage in these areas. In publication II, we allowed haemorrhages extending to multiple areas to be classified in multiple locations. In publication III, haemorrhages situated mainly in the cerebellum were classified as intracerebellar hemorrhages.

5.2.3 *Treatment*

Operated patients were more often treated in the ICU or acute stroke unit (p<0.001), with a median duration of 6 days (versus 1 day in conservatively treated patients). In addition, operated patients had greater frequencies of ventricular drainage and tracheostomy. Total length of hospital stay before in-hospital death, referral to a rehabilitation facility, or discharge to home was also significantly longer in surgically treated patients (p < 0.001) (Table 11).

Table 11. Differences in treatment of conservatively and surgically treated patients.

	All patients (n=1075)	**Conservative treatment (n=967)**	**Surgical treatment (n=108)**	**p**
Ventricular drainage, n (%)	48 (4.5%)	20 (2.1%)	28 (25.9%)	< 0.001
Tracheostomy, n (%)	55 (5.1%)	18 (1.9%)	37 (34.3%)	< 0.001
Treated in ICU or acute stroke unit, n (%)	593 (55.2%)	496 (51.3%)	97 (89.8%)	< 0.001
ICU and acute stroke unit days, median (IQR)	1 (0-4)	1 (0-3)	6 (3-10)	< 0.001
Hospital days, median (IQR)	9 (3-14)	8 (3-14)	13 (7-21)	< 0.001

5.2.4 *Short- and long-term mortality*

We did not observe a significant difference in the functional outcome at hospital discharge between surgically and conservatively treated patients (p=0.155). In addition, no significant differences emerged in in-hospital or 12-month mortality between surgically and conservatively treated patients. The 3-month mortality was significantly lower in surgically treated patients, but the difference disappeared during the follow-up. Mean follow-up was significantly longer in surgically treated patients (p < 0.001) (Table 12).

In Kaplan-Meier analysis of long-term mortality between surgically and conservatively treated patients, the operated patients' long-term survival was significantly better (p = 0.005) with a median survival time of 10.22 years (95% CI 6.73-13.71) versus 4.62 years (95% CI 3.69-5.55) (Figure 7A).

When considering only the propensity score-matched patients, the difference was even more pronounced (p < 0.001) with a median survival time of 8.95 years (95% CI 6.62-11.29) versus 0.06 years (95% CI 0-3.91) (Figure 7B).

Table 12. Differences in outcome of conservatively and surgically treated patients.

	All patients (n=1073)	Conservative treatment (n=965)	Surgical treatment (n=108)	p
Mortality in hospital, n (%)	273 (25.4%)	253 (26.2%)	20 (18.5%)	0.081
mRS at discharge, survivors, median (IQR)	4 (3-5)	4 (3-5)	5 (4-5)	0.155
Mortality at 3 months, n (%)	393 (36.6%)	324 (33.6%)	24 (22.2%)	0.017
Mortality at 12 months, n (%)	384 (32.6%)	359 (37.2%)	34 (31.5%)	0.242
Follow-up length in years, mean (95% CI)	2.41 (2.26-2.55)	2.26 (2.11-2.40)	3.79 (3.14-4.44)	< 0.001

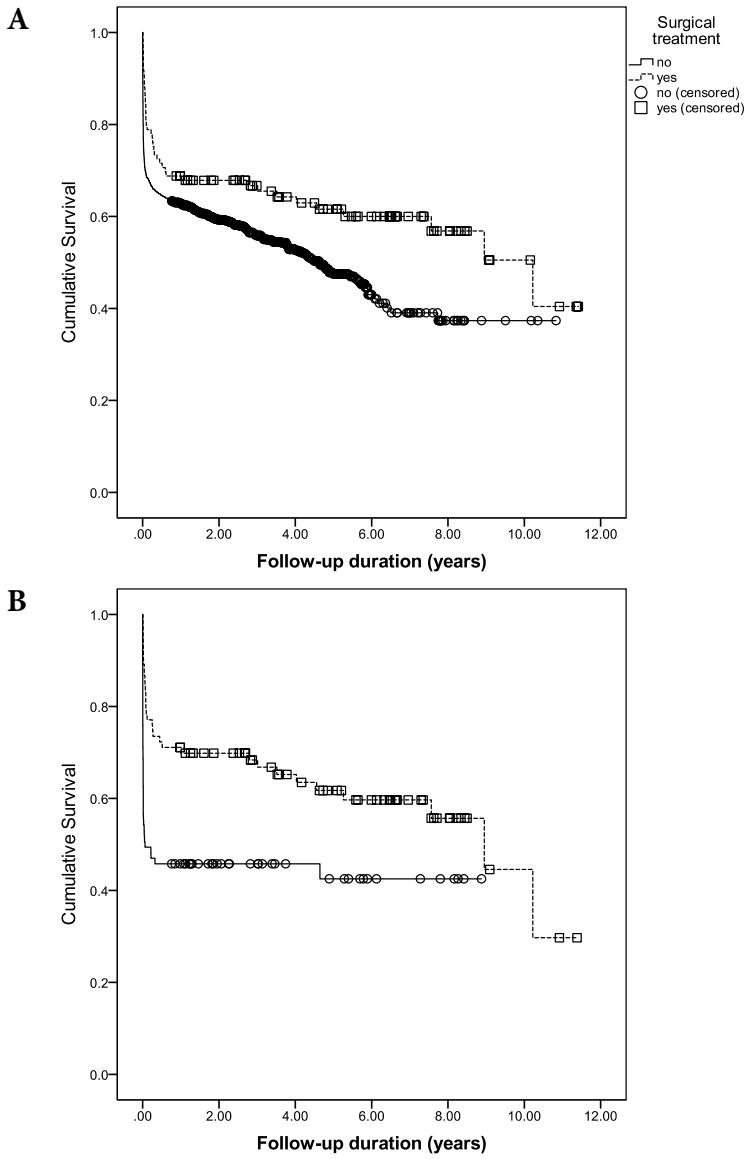


Figure 7A. Differences in long-term mortality of all surgically and conservatively treated patients. **B**. Long-term mortality in propensity-matched cohorts of conservatively and surgically treated patients.

In the Cox proportional hazards model, the proportionality assumption was met with all other variables (age group, GCS on arrival, and ICH volume) except ICH location, which was therefore omitted from the regression model. In univariate regression, lower GCS on admission, increasing age, greater haematoma volume, and haemorrhage location in the brainstem were associated with a greater risk of death in long-term follow-up (Figure 8A-C). In multivariable regression, the results did not change, with age over 80 years being associated with a 9-fold risk of death (Table 13 and Figure 8D).

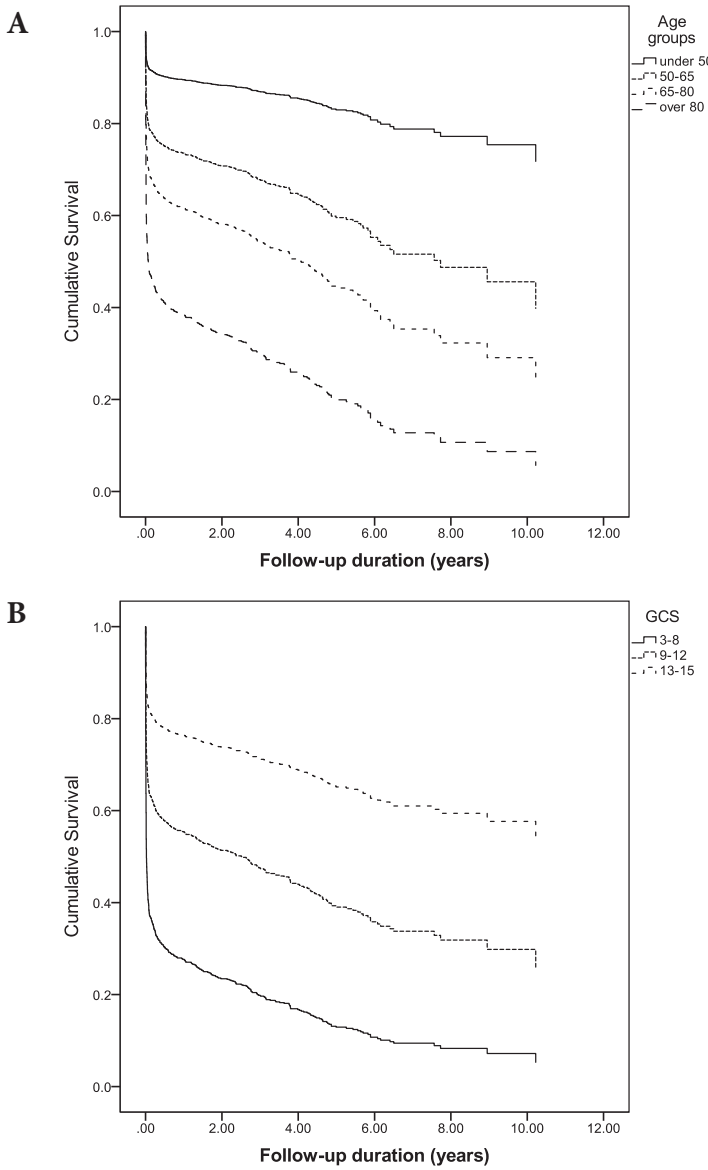
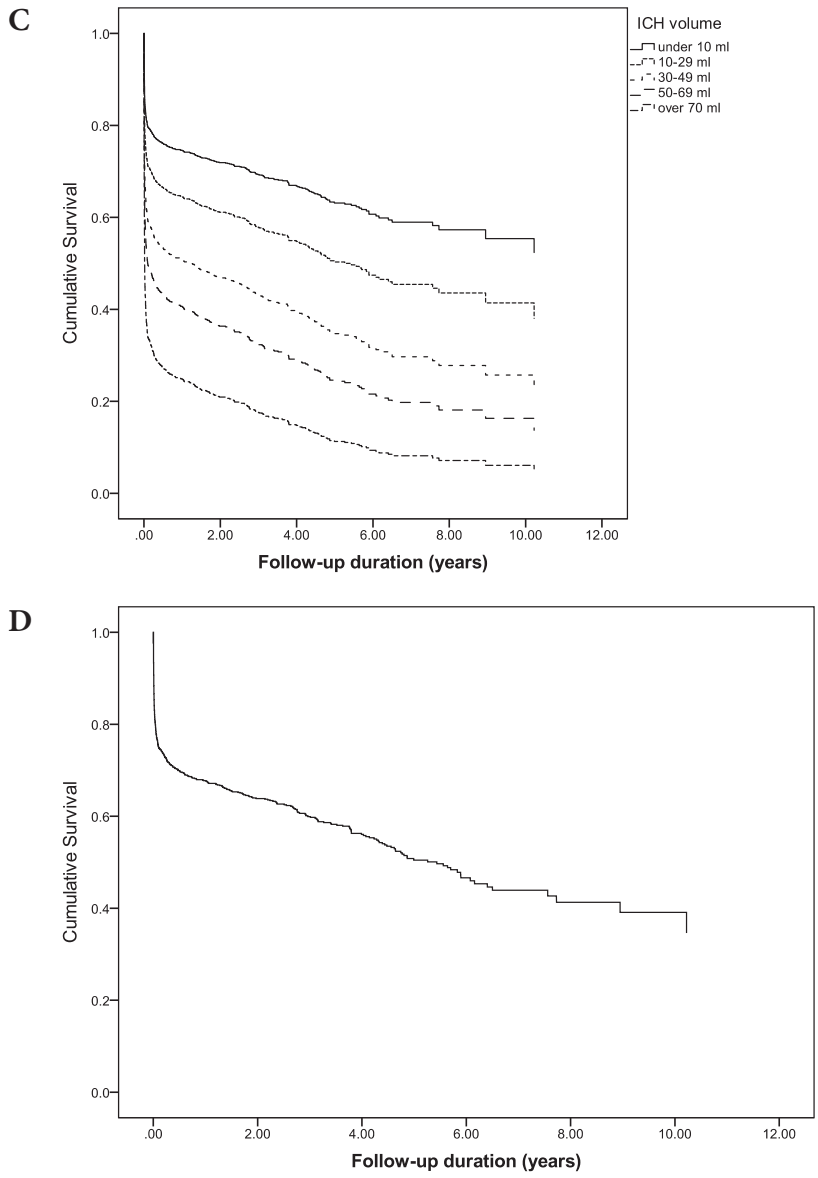


Figure 8A. Survival in different age groups (all patients), univariate Cox regression.
B. Survival in groups by GCS on arrival (all patients), univariate Cox regression.



C. Survival in groups with different ICH volume (all patients), univariate Cox regression.
D. Survival in the multivariable Cox regression model (all patients).

Table 13. Univariate and multivariable results of the Cox proportional hazards model on long-term mortality after ICH.

Variable	Categories	Multivariable HR (95% CI)	p	Univariate HR (95% CI)	p
GCS	13-15	1 (reference)		1 (reference)	
	9-12	1.858 (1.45-2.38)	< 0.001	2.197 (1.73-2.79)	< 0.001
	3-8	3.244 (2.59-4.06)	< 0.001	4.78 (3.92-5.83)	< 0.001
ICH volume	< 10 ml	1 (reference)		1 (reference)	
	10-29 ml	1.414 (1.11-1.80)	0.005	1.493 (1.19-1.88)	0.001
	30-49 ml	1.965 (1.46-2.64)	< 0.001	2.299 (1.76-3.00)	< 0.001
	50-69 ml	2.476 (1.73-3.54)	< 0.001	3.070 (2.19-4.31)	< 0.001
	> 70 ml	3.431 (2.54-4.63)	< 0.001	4.743 (3.62-6.21)	< 0.001
Age group	< 50 years	1 (reference)		1 (reference)	
	50-64 years	2.796 (1.73-4.51)	< 0.001	2.779 (1.72-4.49)	< 0.001
	65-79 years	4.870 (3.07-7.74)	< 0.001	4.371 (2.75-6.94)	< 0.001
	> 80 years	8.814 (5.49-14.16)	< 0.001	8.649 (5.38-13.9)	< 0.001

Table 14. Mortality in the different locations at different time points.

	In-hospital mortality, n (%)	3-month mortality, n (%)	12-month mortality, n (%)
Cortical	61 (18.8%)	81 (25.0%)	100 (30.9%)
Deep	141 (24.6%)	187 (32.6%)	206 (35.9%)
Brainstem	46 (71.9%)	48 (75.0%)	48 (75.0%)
Cerebellum	22 (21.2%)	27 (26.0%)	34 (32.7%)
Intraventricular	3 (33%)	5 (55.6%)	5 (55.6%)

5.3 Intracerebellar haemorrhage (Publication II)

In publication II, we showed that no significant differences existed in either in-hospital nor long-term mortality between surgically and conservatively treated patients, although a non-significant trend towards better survival in the surgical treatment group emerged. However, operated patients more often remained in poor clinical condition.

5.3.1 Demographics and presentation

Of the 1075 patients with a non-traumatic, non-aneurysmal ICH, 114 (10.9%, 47 female) presented with an intracerebellar haemorrhage. Thirty-eight patients (33.3%) were operated on and 76 (66.7%) were managed conservatively. Of the 10 patients with a mainly intracerebellar haemorrhage extending to the brainstem, one underwent surgical treatment and nine were treated conservatively.

As in analyses including all patients with an ICH, those patients with an intracerebellar ICH who underwent surgical treatment were younger and had less atrial fibrillation and hypertension than conservatively treated patients (Table 15). However, their clinical condition on arrival was significantly worse. Surgically treated patients had larger ICHs and more frequent hydrocephalus, quadrigeminal cistern effacement, fourth ventricle obstruction, and brainstem compression (Table 16).

Table 15. Demographics and comorbidities in surgically and medically treated patients with an intracerebellar haemorrhage.

	Medical treatment (n=76)	Surgical treatment (n=38)	p
Male gender, n (%)	45 (59.2%)	22 (57.9%)	0.893
Age in years, mean (95% CI)	71.6 (68.9-74.4)	61.7 (57.6-65.8)	< 0.001
Atrial fibrillation	16 (20.8%)	0	0.03
Hypertension	54 (71.1%)	18 (47.4%)	0.013
Diabetes	17 (22.4%)	3 (7.9%)	0.055
Liver disease	5 (6.6%)	2 (5.4%)	0.808
Heavy drinking	7 (13.5%)	5 (19.2%)	0.506
Warfarin	12 (15.8%)	3 (7.9%)	0.24
Any antiplatelet drug	20 (26.7%)	7 (18.4%)	0.332
Statins	12 (16.2%)	5 (13.2%)	0.669
mRS at arrival, median (IQR)	0 (0)	0 (0)	0.296

Table 16. Clinical and radiological characteristics on arrival in surgically and medically treated patients with an intracerebellar haemorrhage.

	Medical treatment (n=76)	Surgical treatment (n=38)	p
GCS on arrival, median (IQR)	15 (8-15)	6 (3-14)	< 0.001
Systolic BP on arrival, mean (95% CI)	174 (166-182)	188 (174-202)	0.065
Haematoma volume in ml, mean (95% CI)	12.7 (9.9-15.5)	30.4 (25.3-35.4)	< 0.001
Intraventricular blood, n (%)	37 (48.7%)	27 (71.1%)	0.023
Hydrocephalus, n (%)			< 0.001
No	36 (47.4%)	0	
'Beginning'	14 (18.4%)	11 (28.9%)	
'Moderate'	16 (21.1%)	16 (42.1%)	
'Severe'	10 (13.2%)	11 (28.9%)	
Fourth ventricle, n (%)			< 0.001
Open	18 (23.7%)	0	
Compressed	25 (32.9%)	5 (13.2%)	
Blocked	33 (43.4%)	33 (86.8%)	
Quadrigeminal cistern, n (%)			< 0.001
Open	42 (55.3%)	2 (5.3%)	
Compressed	20 (26.3%)	20 (52.6%)	
Blocked	14 (18.4%)	16 (42.1%)	
Brainstem compression, n (%)	24 (31.6%)	35 (92.1%)	< 0.001

5.3.2 Treatment of patients with an intracerebellar haemorrhage

Of surgically treated patients, 92.1% were treated in the ICU or acute stroke unit for at least 24 hours, compared with 55.3% in the conservatively treated group ($p < 0.001$). The surgically treated patients stayed longer in the ICU or stroke unit (median 8 days [IQR 5-11] versus 1 day [0-4], $p < 0.001$) and their total hospital stay (before in-hospital death, referral to a rehabilitation facility or discharge to home) was also longer (median 16 days [IQR 10-26] versus 7 days [2-13], $p < 0.001$). The frequency of tracheostomies was also significantly greater in surgically treated patients (63.2%, 24 patients) than in conservatively managed patients (2.6%, 2 patients) ($p < 0.001$).

5.3.3 *Outcomes and outcome modifiers*

In-hospital mortality was 31.6% (24 patients) in medically and 18.4% (7 patients) in surgically treated patients, but the difference was not significant (p = 0.137). Long-term mortality was 50% in medically and 47.4% in surgically treated patients (p = 0.791). Mean follow-up length was 27.3 months (95% CI 20.7-33.8 months) in medically and 45.7 months (95% CI 31.9-59.6 months) in surgically treated patients. The difference was significant (p=0.005). In Kaplan-Meier analysis, we did not find a significant difference in long-term mortality between the treatment groups (p=0.184), with a median survival time of 4.64 years (95% CI 1.67-7.62 years) in the conservative treatment group and 8.95 years (95% CI 0.54-17.36 years) in the surgical treatment group (Figure 9). However, the clinical outcome of the surviving patients at hospital discharge was significantly worse in the surgically treated group – the median mRS with interquartile ranges was 4 (3-4) in the medically and 5 (4-5) in the surgically treated group (Figure 10). The difference was significant (p<0.001).

To assess the effect of different factors on poor outcome or death (mRS 4-6) at hospital discharge, we constructed a multivariable regression model (Table 17). GCS <8 (OR 366.1, 95% CI 1.84-3270000, p = 0.023) and age group 65-79 years (OR 113.2, 95% CI 2.27-12700000, p = 0.012) were associated with poor outcome. Due to small sample size, some of the confidence intervals were unrealistic.

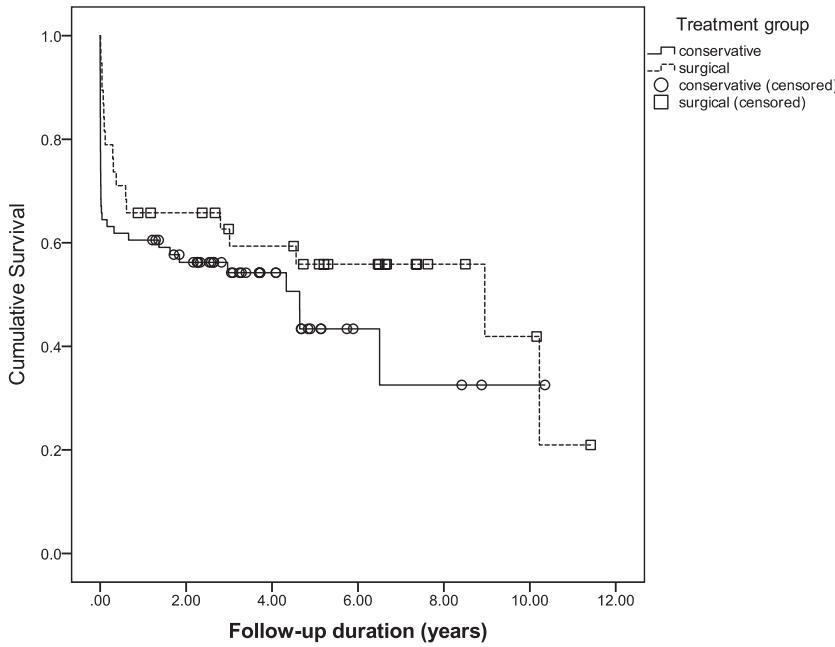


Figure 9. Kaplan-Meier analysis of long-term mortality in the two treatment groups. The difference was insignificant (p=0.184).

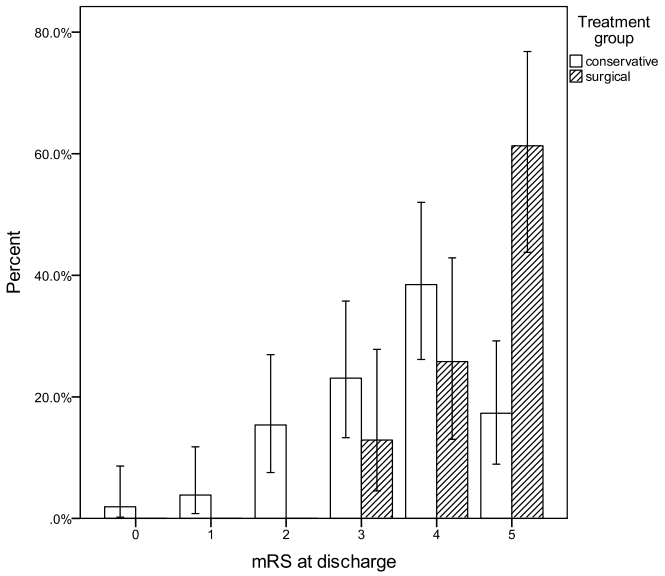


Figure 10. Functional outcome of surviving patients (n=30 in operative group, n=53 in conservative group) at hospital discharge. The error bars represent 95% confidence intervals. The difference was significant (p<0.001).

Table 17. Results of univariate logistic regression on poor functional outcome and mortality (modified Rankin Scale 4-6).

Variable		**Odds Ratio**	**95% CI**	**p**
Age group	Under 50	reference		
	50-64	1.647	0.064-626	0.765
	65-79	113.2	2.27-12700000	0.012
	Over 80	48.04	0.812-6200000	0.067
GCS at arrival	13-15	reference		
	8-12	9.767	0.345-2180	0.175
	3-7	366.1	1.84-3270000	0.023
Ventricular blood		11.31	0.838-3530	0.073
Brainstem compression		6.586	0.293-3230	0.236
Volume > 10 ml		0.399	0.017-5.6	0.496
Diameter > 3 cm		3.145	0.337-52.9	0.317
Extension to brainstem		5.094	0.045-5550	0.51
Hydrocephalus	No	reference		
	'Beginning'	5.589	0.401-2280	0.211
	'Moderate'	8.82	0.441-799	0.167
	'Severe'	90.83	0.853-1580000	0.06
Fourth ventricle	Open	reference		
	Compressed	3.939	0.51-51.5	0.202
	Blocked	0.3738	0-17.2	0.631
Quadrigeminal cistern	Open	reference		
	Compressed	1.068	0.063-100	0.965
	Blocked	1.635	0.008-2400	0.851
Surgical treatment		1.98	0.098-1010	0.662

5.4 ICH-related hydrocephalus (Publication III)

In publication III, we showed that hydrocephalic patients were in significantly worse clinical condition, had larger ICHs, and had more frequent intraventricular haemorrhage than patients who did not have hydrocephalus. In-hospital and 3-month mortality were lower in those patients who received surgical treatment for hydrocephalus. In a propensity score-matched comparison, surgical treatment of hydrocephalus was associated with a 50% lower 3-month mortality than non-surgical treatment.

5.4.1 Demographics and presentation

Of the 1075 patients, 105 patients (9.8%) had 'beginning', 112 (10.4%) 'moderate', and 79 (7.3%) 'severe' hydrocephalus on the Stein classification. No differences were present in the age or gender distribution between non-hydrocephalic and hydrocephalic patients, but patients with abnormal ventricular size were in significantly worse clinical condition, had larger haematomas, and had more frequent IVH. The haemorrhages were more often situated in the cerebellum, basal ganglia, and brainstem and less often in the lobar region (Table 18). Compared with non-hydrocephalic patients, the in-hospital and 3-month mortalities were higher in hydrocephalic patients, and they were left in a significantly worse clinical condition after a significantly longer period in the hospital before in-hospital death, transfer to a rehabilitation facility/hospice, or discharge to home (Table 19).

Table 18. Differences between ICH patients with normal ventricular size and hydrocephalus. Patients with 'beginning' hydrocephalus on the Stein classification were defined as hydrocephalic. Patients were included in multiple location categories if the haematoma extended to multiple territories.

Variable	**No hydrocephalus (n=777)**	**Hydrocephalus (n=298)**	**p**
Age in years, mean (95% CI)	67.7 (66.7-68.6)	66.7 (65.1-68.2)	0.26
Female gender, n (%)	329 (42.3%)	128 (43%)	0.856
GCS on arrival, median (IQR)	15 (12-15)	7 (3-14)	< 0.001
Systolic BP in mmHg, mean (95% CI)	173 (171-176)	175 (171-180)	0.481
ICH volume in ml, mean (95% CI)	17.3 (15.7-19)	46.1 (40.7-51.4)	< 0.001
Lobar, n (%)	572 (73.6%)	126 (42.3%)	< 0.001
Basal ganglia, n (%)	131 (16.9%)	69 (23.2%)	0.018
Brainstem, n (%)	38 (4.9%)	26 (8.7%)	0.017
Cerebellum, n (%)	34 (4.4%)	79 (23.5%)	< 0.001
Only IVH, n (%)	2 (0.3%)	7 (2.3%)	0.001
Intraventricular blood, n (%)	217 (21.7%)	258 (86.6%)	< 0.001

Table 19. Treatment and outcomes in patients with and without hydrocephalus.

Variable	**No hydrocephalus (n=777)**	**Hydrocephalus (n=298)**	**p**
Haematoma evacuation (all locations), n (%)	44 (5.7%)	64 (21.5%)	< 0.001
Hospital days, median (IQR)	9 (4-15)	5 (1-13)	< 0.001
Mortality in hospital, n (%)	110 (14.2%)	163 (54.7%)	< 0.001
mRS at discharge, median (IQR)	4 (2-5)	5 (4-5)	< 0.001
Mortality at 3 months, n (%)	159 (20.5%)	189 (63.4%)	< 0.001

5.4.2 Surgical treatment for hydrocephalus

We then examined the 298 hydrocephalic patients in detail. In total, 61 patients (20.5%) received surgical treatment for hydrocephalus, i.e. either received an EVD (n=47, 77%) and/or underwent cerebellar ICH evacuation (n=42, 68.9%). The surgically treated patients were younger, their premorbid functional status was slightly better, and they had smaller haemorrhages. No statistically significant differences existed in clinical status on arrival. The patients who received surgical treatment for hydrocephalus had more often cerebellar haemorrhages, and less often cortical and deep hemispheric haemorrhages. They also had lower median IVH scores and more often moderate or severe hydrocephalus. Due to their dismal clinical situation, 58 patients (79%) with severe hydrocephalus did not receive surgical treatment (Table 20).

Table 20. Differences in hydrocephalic patients who did or did not receive surgical treatment for hydrocephalus.

Variable	**No surgical treatment for hydrocephalus (n=237)**	**Surgical treatment for hydrocephalus (n=61)**	**p**
Age in years, mean (95% CI)	68.1 (66.4-69.8)	61.1 (57.8-64.5)	0.001
Female gender, n (%)	101 (42.6%)	27 (44.3%)	0.817
mRS before arrival, median (IQR, range)	0 (0-1, range 0-5)	0 (0, range 0-3)	0.014
GCS on arrival, median (IQR)	7 (3-13)	6 (3-14)	0.986
ICH volume in ml, mean (95% CI)	51.2 (44.7-57.6)	26.3 (21.9-30.7)	0.002
Lobar, n (%)	120 (50.6%)	6 (9.8%)	< 0.001
Thalamic, n (%)	61 (25.7%)	8 (13.1%)	0.037
Brainstem, n (%)	23 (9.7%)	3 (4.9%)	0.237
Cerebellum, n (%)	29 (12.2%)	41 (67.2%)	< 0.001
Only IVH, n (%)	4 (1.7%)	3 (4.9%)	0.137
Intraventricular blood, n (%)	210 (88.6%)	48 (78.7%)	0.043
IVH score, median (IQR)	5 (2-7)	4 (2-5)	0.001
Hydrocephalus severity, n (%)			0.028
'Beginning'	93 (39.2%)	12 (19.4%)	
'Moderate'	85 (35.9%)	27 (44.3%)	
'Severe'	58 (24.5%)	21 (34.4%)	

Compared with patients who did not receive surgical treatment for hydrocephalus, the patients whose hydrocephalus was treated surgically underwent haematoma evacuation (all locations) more frequently (68.9% vs 9.3%, p < 0.001), stayed longer in the ICU or acute stroke unit (median 7 days [IQR 3-12] vs 0 days [0-3], p < 0.001), and had longer hospital stay (median 16 days [IQR 8-26] vs. 3 days [1-8], p < 0.001).

5.4.3 *Outcome after surgical treatment for hydrocephalus*

Compared with patients whose hydrocephalus was treated conservatively, those who received surgical treatment for hydrocephalus had significantly lower in-hospital (19.7% vs. 63.7%, p < 0.001) and 3-month mortality (27.9% vs. 72.6%, p < 0.001). No difference existed in functional outcome at hospital discharge; it was poor in both groups (median 5 [IQR 4-5], p=0.206).

We then used a propensity model to compare the effect of the surgical treatment for hydrocephalus in similar patient groups. Three patients with a haemorrhage extending to the brainstem were excluded. In the 66 propensity-matched patients (33 in both groups), 3-month mortality was significantly lower in patients undergoing surgical treatment for hydrocephalus than in those who did not (33.3% vs. 66.7%, p = 0.007), while no differences were observed in the variables used to construct the propensity score (Table 21).

Table 21. Propensity score-matched comparison between patients with surgical treatment for hydrocephalus, either with EVD or cerebellar haematoma evacuation, and patients without surgical treatment. The variables denoted with an asterisk were not included in the calculation of the propensity score.

Variable	**No surgical treatment for hydrocephalus (n=33)**	**Surgical treatment for hydrocephalus (n=33)**	**p**
Age in years, mean (95% CI)	67.0 (61.0-73.0)	64.0 (59.6-68.4)	0.373
Haematoma volume in cm3, mean (95% CI)	20.1 (14.2-26.0)	27.7 (21.0-34.3)	0.082
Cerebellar ICH	18 (54.5%)	18 (54.5%)	1
GCS 3-8 on arrival, n (%)	15 (54.5.2%)	15 (54.5%)	1
Moderate or severe hydrocephalus, n (%)	26 (78.8%)	28 (84.8%)	0.523
GCS on arrival, median (IQR) *	11 (3-15)	11 (3-14)	0.657
IVH score, median (IQR) *	4 (1-7)	4 (2-6)	0.477
Hydrocephalus severity, n (%) *			0.668
'Beginning'	7 (21.2%)	5 (15.2%)	
'Moderate'	17 (51.5%)	17 (51.5%)	
'Severe'	9 (27.3%)	11 (33.3%)	
3-month mortality *	22 (66.7%)	11 (33.3%)	0.007

5.4.4 Complications and shunt placement

The median duration of EVD treatment was 7 days (IQR 3-11). Seven patients needed one EVD change, while one patient needed four catheter changes because of clogging. One patient received intraventricular rTPA to open a clogged EVD. Four patients (8.5%) had EVD-related meningitis, all treated with ceftazidime and vancomycin. Two patients received a lumbar drain for persistent hydrocephalus, and one of these was later shunted. In total, only six patients of 1075 received a shunt (0.6%). The median interval between ICH and shunt insertion was 12 days (IQR 0-22). Two shunts needed revision; one was externalised and later revised because of clogging, and one patient underwent shunt valve replacement because the initial valve resistance was too high.

5.5 ICH in the young (Publication IV)

In publication IV, we used a separate data of 325 patients aged between 16 and 49 years that also included haemorrhages with macrovascular/structural causes. All consecutive patients admitted during a 10-year period, from January 2001 to March 2010, were included. We showed that surgical haematoma evacuation predicted a significantly lower 3-month mortality relative to patients treated conservatively (OR 0.06, 95% CI 0.02-0.21, p < 0.001).

5.5.1 Demographics and radiological findings

Patients' median age was 42 years (IQR 34-47), with a slight (59.5%) male predominance. Using the SMASH-U classification[3], the aetiology was hypertensive microangiopathy in 84 patients (26%), structural in 84 (26%), other (including systemic diseases) in 52 (16%), and unknown in 105 (32%). Of the structural haemorrhages, the bleed was caused by an AVM in 45 patients (13.4%), and by a cavernous angioma in 36 patients (10.7%). The median ICH volume was 11 ml (IQR 3-36 ml), and in 34.8% of the patients the haemorrhage extended to the ventricles. The majority of the patients were in good condition, the median GCS on arrival being 15 (IQR 10-15).

5.5.2 Treatment

In total, 102 patients (31.4%) underwent craniotomy and haematoma evacuation. In addition, 6 patients (1.8%) needed a primary decompressive hemicraniectomy. Thirty-one patients (9.5%) received an EVD. Of the patients, 32% were treated in an acute stroke unit, 53% in a general or neurosurgical specialist ICU, and the remaining 15% in a neurological or neurosurgical ward.

5.5.3 Predictors of three-month mortality

The 3-month mortality was 16.9%. Treatment was withdrawn in 46 patients (13.7%) and 22 patients were eligible as potential organ donors. At discharge, 37.5% of patients were functionally independent (mRS 0-2).

In multivariable regression, increasing NIHSS score, infratentorial location, hydrocephalus, multiple haemorrhages, and radiological herniation were statistically significant predictors of mortality at 3 months. By contrast, haematoma evacuation was significantly associated with better probability of survival (OR 0.06, 95% CI 0.02-0.21, p < 0.001) (Table 22).

Because of differences between the operated and conservatively treated patient groups, we used a propensity score for matching the surgically and conservatively treated patients. In the matched patients, haematoma evacuation was associated with 71% lower 3-month mortality (7.8% vs 27.5%, p < 0.001), even though the operated patients had larger haematomas and more frequent radiological herniation (Table 23).

Table 22. Results of the multivariate regression for 3-month mortality.

Variable	OR	95% CI	p
Female sex	1.13	0.43-3.00	0.803
Age groups in years			
16-29	1 (reference)		
30-39	0.06	0.01-0.35	0.002
40-49	0.19	0.05-0.75	0.017
NIHSS on arrival			
0-6	1 (reference)		
7-14	6.25	1.23-31.8	0.027
>14	39.00	7.77-196	< 0.001
Location			
Lobar	1 (reference)		
Basal ganglia	1.74	0.35-8.65	0.501
Infratentorial	13.89	2.33-82.8	0.004
Volume in ml			
0-29	1 (reference)		
30-60	1.84	0.56-6.02	0.315
> 60	1.84	0.38-8.88	0.449
Intraventricular blood	2.07	0.77-5.58	0.152
Hydrocephalus	4	1.61-9.9	0.003
Multiple haemorrhages	6.82	1.65-28.20	0.008
Radiological herniation	5.94	1.71-20.6	0.005
Haematoma evacuation	0.06	0.02-0.21	< 0.001

Table 23. Differences in propensity-matched surgically and conservatively treated patients.

Variable	ICH evacuation (n=102)	Conservative treatment (n=102)	p
Female sex, n (%)	41 (40.2%)	39 (38.2%)	0.774
Age groups, n (%)			0.876
16-29	23 (22.5%)	20 (19.6%)	
30-39	23 (22.5%)	24 (23.5%)	
40-49	56 (54.9%)	58 (56.9%)	
NIHSS score, n (%)			0.392
<6	39 (38.2%)	46 (45.1%)	
6-14	17 (16.7%)	11 (10.8%)	
>14	46 (45.1%)	45 (44.1%)	
Non-structural etiology, n (%)	60 (58.8%)	61 (59.8%)	0.887
Location, n (%)			0.096
Lobar	19 (18.6%)	24 (23.5%)	
Basal ganglia	29 (28.4%)	37 (36.3%)	
Infratentorial	18 (17.6%)	21 (20.6%)	
Mixed	36 (35.3%)	20 (19.6%)	
ICH volume, n (%)			0.002
0-29 ml	48 (47.1%)	65 (63.7%)	
30-60 ml	23 (22.5%)	26 (25.5%)	
>60 ml	31 (30.4%)	11 (10.8%)	
Intraventricular blood, n (%)	42 (41.2%)	37 (36.3%)	0.472
Hydrocephalus, n (%)	33 (32.4%)	26 (25.5%)	0.280
Multiple haemorrhages, n (%)	3 (2.9%)	5 (4.9%)	0.471
Radiological herniation, n (%)	28 (27.5%)	16 (15.7%)	0.041
Mortality at 3 months, n (%)	8 (7.8%)	28 (27.5%)	< 0.001

6 DISCUSSION

6.1 Main findings

Different prognostic scores for ICH abound in the literature, but the familiar and clinically widespread NIHSS score performed as well as the best dedicated prognostic scores in estimating the risk of in-hospital death. For 3- and 12-month mortality, the new ICH Functional Outcome Scale (ICH-FOS)[193] performed best.

In addition, we showed that surgical treatment of ICH was beneficial, especially in certain subpopulations. When considering all patients with ICH, surgically treated patients had significantly lower long-term mortality than conservatively managed patients, and the difference became more pronounced in a propensity score-matched comparison.

However, surgically treated patients with an intracerebellar haemorrhage did not show better short- or long-term survival than the ones treated conservatively. Surgery may have saved the patients' lives, but the functional outcome was significantly worse in the surgically treated patients, similarly as shown in patients with a deep ICH already in the late 1980s at Helsinki University Hospital[11].

ICH-related hydrocephalus was a clear predictor of high mortality and poor outcome, at least when left untreated. When the ICH-related hydrocephalus was treated surgically by external ventricular drainage, shunt insertion, or evacuation of a cerebellar haemorrhage causing the hydrocephalus, the 3-month mortality was significantly lower. In a propensity score matched comparison, surgical treatment of hydrocephalus was associated with a 50% lower mortality than conservative treatment.

In the young, surgical evacuation of ICH was associated with a significantly lower 3-month mortality. Predictors of increased 3-month mortality did not differ from the previously known ones, including increasing symptom severity, infratentorial location, hydrocephalus, radiological herniation, and presence of multiple haemorrhages.

6.2 Use of prognostic scores for ICH

In publication I, we found a total of 19 different prognostic scores and models for outcome or mortality estimation after ICH. Our study was the first to include all of the published models, making them comparable in a large, single-centre cohort of consecutive ICH patients. The NIHSS score performed astonishingly well in predicting in-hospital after ICH (AUC 0.825, 95% CI 0.790-0.860), while the ICH Functional Outcome Score (ICH-FOS) was superior for 3-month and 12-month mortality (AUC 0.88 [95% CI 0.855-0.906] and 0.864 [0.838-0.891], respectively). In our analyses, most of the scores performed reasonably well, with only the Tuhrim equation giving an AUC < 0.7 for 3-month mortality.

The National Institutes of Health Stroke Scale was originally created to assess neurological impairment severity in ischaemic stroke patients, but it has since been validated for ICH as well[207]. It seems logical that the presentation neurological status should be predictive of outcome, at least short-term, and the finding is in line with previous results which suggest that GCS could suffice for outcome prediction in ICH patients[208]. The ICH-FOS score includes both GCS and NIHSS scores as score components, reinforcing the importance of current neurological status and level of consciousness in outcome prediction. In addition to ICH-FOS, NIHSS was included in the modified and new ICH scores[187], the Essen ICH score[188], and the Get With The Guidelines (GWTG) score[168]. These do not, however, report the prognostic performance of the score components.

In ischaemic stroke, experienced clinicians' ability to correctly predict 30-day mortality may be as low as 33.1%[209], and compared with this figure, all of the scores performed extremely well. The three mathematical

models – Cincinnati model[172], Masé model[173], and Tuhrim equation[174] – seem hard to implement in day-to-day clinical usage, although nowadays using a smartphone app or a comparable calculator software might overcome this obstacle. Although there are no published data on the clinical usage of the different scores, to our knowledge, only the ICH score is in widespread clinical use.

Many of the scores seem to include the same variables as the original ICH score, with slight differences in point assignments. In addition to GCS as a measure of level of consciousness, the original ICH score includes age, infratentorial location, ICH volume, and intraventricular extension.[9] The ICH-FOS score adds NIHSS, reinforcing the value of current clinical neurological status, and hyperglycemia as a sign of uncontrolled diabetes.[193] Hydrocephalus has been found to be a significant predictor of poor outcome, but it was not included in any of the scores.[144] One explanation may be that ICH-related hydrocephalus is usually caused by intraventricular or infratentorial haemorrhage, both of which are incorporated in most prognostic models.

Each new score aims at improving prognostication in all or some subgroups of ICH patients - patients in hemodialysis[210], patients in developing countries[149], or a highly selected cohort for surgical intervention[206]. However, many of the scores have been developed based on very small or very selected patient cohorts, and while they are mainly based on the original ICH score, differences in the point assignments may be statistical consequences of differences in the small derivation cohorts. In addition, some outcomes seem to be defined *a posteriori*. Most of the scores also use dichotomised or categorised variables, which may cause loss of information and statistical power.[182]

Selection of the score components in the 19 models generally seems to have been based on choosing the "most significant" variables in univariate analyses to be included in the regression model. In some circumstances, this could be helpful in finding new explanatory variables, but it may also result in omitting variables that are usually significant but not in the derivation cohort, known as statistical "over-fitting".[211] In publication I, we observed that the predictive performance of the ICH-FOS score for 12-month mortality was in our analyses higher than in the original article (AUC 0.830 vs. 0.8642), and it seems that the ICH-FOS score was not statistically over-fitted to the derivation population.[193]

Many authors have expressed concerns about "self-fulfilling prophecies" in connection with the prognostic scores.[194,212-215] Leaving patients with a suspected poor prognosis without proper treatment probably accounts for an inevitable death, and if this has been done in the derivation cohorts, the model will inherently produce an estimate of a poor prognosis for similar patients.[212] However, not only decisions to withhold treatment affect the prognostic model – all hidden confounders in the derivation cohorts are projected in the estimates produced by the prognostic model and may incorporate some unaccounted bias into the results. At our institute, a new policy to guarantee all ICH patients with a suspected poor prognosis a possibility of admission to ICU minimises the risk of "too hasty" end-of-life decisions and has, in addition, increased the number of potential organ donors substantially [216].

In our opinion, the prognostic scores may be helpful in scientific work, e.g. as inclusion criteria for prospective trials, but one should remain cautious in applying the results in individual patients in clinical work and when communicating the risk of death to patients and relatives. The scores pose an ethical dilemma but do not give an answer – could there ever be such a threshold produced by a mathematical model alone, after which the treatment could or should be considered futile?

6.3 Surgical treatment of intracerebellar haemorrhage

In publication II, we studied a group of 114 patients with a cerebellar ICH. Our aim was to compare functional outcome and long-term mortality in medically and surgically treated patients.

Since the 1970s, a mutual understanding has existed among neurologists and neurosurgeons that large (diameter over 3 cm) intracerebellar haemorrhages need to be evacuated in patients with a declining level of consciousness.[137] This results in an innate selection bias towards patients with larger ICHs and more severe symptoms in the surgical group.

This was reflected in publication II. Significant differences were present in the baseline characteristics of surgically and conservatively treated patients. The operated patients were younger, had larger haemorrhages, and had lower level of consciousness on arrival. They suffered more often from brainstem compression and hydrocephalus. Most patients were first observed before proceeding to surgery, with a mean interval from admission to surgery of 22.7 hours. Older patients with more comorbidities were more often treated conservatively.

No significant differences emerged in short- or long-term mortality between surgically and conservatively treated patients, but the surgically treated patients were left in a significantly worse clinical condition, at least at hospital discharge. In the multivariable logistic regression, age was associated with poor functional outcome at discharge or in-hospital death (mRS 4-6) in the age group of 65-80 years, but not in other age groups. This could be caused by referral bias; some elderly patients in poor condition may have been left in primary hospitals. Hydrocephalus[217,218], brainstem compression[138,219], fourth ventricle obstruction[202], and quadrigeminal cistern obliteration[201] were associated with poor outcome in the univariate analyses, but did not reach significance in the multivariable regression model. Fourth ventricle obstruction or compression is considered the root cause of hydrocephalus in patients with intracerebellar haemorrhage, while quadrigeminal cistern obstruction is thought to represent mass effect in the posterior fossa. In our series, GCS < 13 on admission led to a poor outcome without exception, consistent with previous studies.[140,143,217,219]

Very limited data are available on long-term outcome after cerebellar ICH. In a Swedish study, 62% of patients either died or had an unfavourable outcome in a long term (70-month) follow-up.[217] In publication II, the long-term mortality was 50% in medically and 47.4% in surgically treated patients after a mean follow-up of 34 months. We used mRS 1 to 3 at discharge as a sign of favourable functional outcome, and the incidence was as low as 10.5% in surgically and 30.7% in conservatively treated patients. Dolderer and co-workers have previously reported similar figures, with only 14% of surgically treated patients having a favourable outcome in a long-term (49-month) follow-up.[143] In addition, it has been shown that moderately disabled patients with a cerebellar ischaemic stroke recovered well, but a poor initial condition led to a poor rehabilitation outcome.[220]

Patients with a cerebellar ICH seem to be a group that often undergoes surgical treatment, although the scientific proof of benefits is somewhat vague[15] and treatment results are generally pessimistic.[17] The concept of clinical equipoise means that there is uncertainty in the research community about the superiority of two treatment options, and this allows one to construct a trial testing these two treatments against each other.[221] As surgery is usually considered the standard treatment in patients with a large intracerebellar haemorrhage and declining level of consciousness, clinical equipoise hardly exists. This makes constructing future prospective randomised trials ethically

difficult. However, as we, among others, have shown, surgical treatment results leave much to be desired, and patients are left in such a poor condition that it might be possible to randomise patients to conservative treatment instead of surgery should future investigations produce similar results.

6.4 ICH-related hydrocephalus

In publication III, we compared the hydrocephalic and non-hydrocephalic ICH patients and observed that the hydrocephalic patients had a strikingly high in-hospital and 3-month mortality. Some of the effect was probably due to higher ICH volumes in hydrocephalic patients. These results are in line with previous findings, with the majority of the authors considering ICH-related hydrocephalus a state of very high mortality and a sign of poor outcome.[20,147]

However, in patients who either underwent cerebellar ICH evacuation or received an EVD or a shunt to treat the hydrocephalus, the mortality dropped significantly, approaching the level of non-hydrocephalic patients (27.5% vs. 20.5%). In the propensity score analysis, surgical treatment of ICH-related hydrocephalus was associated with a 50% reduction in mortality.

Previously, small non-lobar ICH, GCS less than 8, and severe IVH have been considered predictors of EVD treatment.[150] In the same study, mortality was significantly higher in patients who received an EVD than in patients who did not receive an EVD. In publication III, our surgically and non-surgically treated patients showed no differences in GCS on arrival, but the haemorrhage volumes were smaller in those patients whose hydrocephalus was treated surgically. In the surgically treated patients, the haemorrhages were more often located in the cerebellum and less often in the cortical or deep hemispheric areas. This reflects both the strategic location of posterior fossa in the pathogenesis of ICH-related hydrocephalus and the high tendency to operate on patients with cerebellar ICHs.[15]

Many of the ICHs in the hydrocephalic patients were situated in the cerebellum, causing not only hydrocephalus but brainstem compression as well. However, in publication II we showed in the same patients that evacuation of an intracerebellar haemorrhage did not cause significant differences in short- or long-term mortality.

We constructed a propensity score to isolate the effect of hydrocephalus and compare mortality in matched pairs of hydrocephalic patients, half of whom received surgical treatment for hydrocephalus, while the other half did not. We observed that in-hospital and 3-month mortality were much lower in the group of surgically treated patients. Although we saw in pairwise comparisons that the conservatively treated patients more often had catastrophic bleeds and distorted, blood-filled ventricles, it is likely that the surgically treated patients would have had a much worse prognosis had they been left without surgical treatment.

In publication III, the frequency of shunts was extremely low – only 0.6% of all patients with ICH or 9.8% of hydrocephalic ICH patients received a shunt. In previous studies, the frequency of shunts in ICH-related hydrocephalus has varied between 20% and 29%.[156,157] We could not assess factors associated with shunt-dependent hydrocephalus due to the low number of patients receiving a shunt.

No good guidelines exist on when to treat ICH-related hydrocephalus or to insert an EVD, and hence, the treatment decisions are always made case-by-case. In an observational retrospective series, it is clear that the populations of treated and untreated patients have significant differences. Some of the differences are explained by referral bias; some of the patients may not have been referred to our hospital because of suspected grim prognosis

or they may have died before arrival. However, despite these shortcomings, we showed in publication III that surgical treatment of non-aneurysmal non-traumatic ICH patients with hydrocephalus was beneficial and associated with a substantially lower in-hospital and 3-month mortality. This raises the question of whether the decision not to offer surgical treatment to hydrocephalic ICH patients could be a self-fulfilling prophecy.[212]

6.5 ICH in the young

In publication IV, we assessed the different predictors of 3-month mortality in patients with ICH aged 16-49 years. Haematoma evacuation was associated with a significantly lower 3-month mortality. In the multivariable regression model for 3-month mortality, haematoma evacuation was associated with an odds ratio of 0.06 (95% CI 0.02-0.21, $p < 0.001$). This was in accordance with previous results; Lai and colleagues observed that haematoma evacuation was associated with mortality in a multivariable regression model with an odds ratio of 0.211 (95%CI 0.09-0.476, $p < 0.001$).[164] When compared with the youngest age group, the age groups 30-39 years and 40-49 years were associated with a reduced risk of mortality in the multivariable regression, with odds ratios of 0.06 (95% CI 0.01-0.35, $p = 0.002$) and 0.19 (95% CI 0.05-0.75, $p = 0.017$), respectively.

We showed that predictors of mortality did not differ from those previously reported for young[164] or older patients: GCS < 8, infratentorial location, intraventricular blood, hydrocephalus, and haematoma volume > 30 ml.[9,144] The total 3-month mortality was 16.9%, significantly lower than the mortality in all ICH patients in publications II and III. In previous studies, the reported mortality has varied between 20.4%[222] and 26.1%[223], although the latter study included aneurysmal ICHs as well.

In total, ICH was evacuated in 31.4% of patients (102 patients), and 1.8% (6 patients) underwent a decompressive craniectomy, one of which was a suboccipital craniectomy for an intracerebellar haemorrhage. In contrast to publications II and III, ICHs originating from macroscopic structural lesions (n=84, 25.8%) were included and 41 (48.8%) of these patients underwent haematoma evacuation.

6.6 Surgical treatment of ICH in the whole study population

When looking at the whole population with a non-traumatic, non-aneurysmal ICH after exclusion of macroscopic vascular/structural haemorrhages, we observed that the 3-month mortality was 36.6% and median survival time was 4.86 years (95% CI 4.07-5.66), compared with corresponding national figures of 35% and 4.5 years.[29] Relative to conservatively treated patients, the long-term mortality was substantially lower in the patients who had undergone ICH evacuation. In Cox proportional hazards univariate analyses, higher age, lower GCS and increasing haematoma volume were significantly associated with a higher risk of death in long-term follow-up. The same observation was made in a multivariable analysis. Other predictors of poor outcome, such as ICH location, hydrocephalus severity, and IVH, did not meet the proportionality assumption and could not be included in the model.

6.7 Strengths and limitations of the study

To the best of our knowledge, our study is one of the largest consecutive single-centre series published. It includes all patients with a spontaneous, non-traumatic, non-aneurysmal ICH treated at our tertiary university teaching hospital during a five-year period. However, due to the observational and retrospective nature of the study, some selection and referral bias surely exist. Patients may not have been

referred to our unit, or they may have died before arrival to hospital. This may apply especially to patients in the oldest age groups, as patients with minor, or the most catastrophic bleeds may have been left in the admitting hospitals. However, as neither neurosurgical treatment nor neurosurgical intensive care was available in other institutions in our area, all patients in need of tertiary-level care and expertise were included in our series. In publication IV, we might not have found all patients with a bleed originating from a tumour, possibly because they were not given an ICH-related ICD-10 code. We did not have a protocol for imaging studies, and therefore, the majority of the patients (86.7%) did not undergo an MRI. In addition, we only used CTA to exclude vascular malformations instead of DSA, which is the gold standard and still superior to CTA, despite the recent advances in CT-based imaging.[224] Autopsies or surgical biopsies were obtained in very few patients. Hence, the aetiological classification may be inaccurate and is mainly based on the concept of 'most likely aetiologies'.[3] Traumatic or aneurysmal haemorrhages were not included in the study, and we decided to exclude haemorrhages related to arteriovenous malformations, cavernous angiomas, and dural fistulae in publications II and III as well.

As no good guidelines exist, criteria for surgical treatment were not protocol- or guideline-based. Instead, the need for a surgical intervention was carefully considered for each patient, weighing the patient's age, level of consciousness, comorbidities, symptoms, and haematoma location. Especially considering surgical treatment of hydrocephalus, the surgically treated patients present only a minor subset of all hydrocephalic patients. However, they seem to have benefited from surgical treatment.

One of the main limitations of the study is the heterogeneity in baseline characteristics of both conservatively and surgically treated patients. As the need for surgery was individually considered for every patient, the surgically treated patients tended to be younger, more symptomatic, and have larger ICHs. Many of these differences explain why the treatment decisions were made. This can be observed especially in the patients with a cerebellar ICH, where the surgically treated patients would probably have died if left untreated. Where suitable, we tried to overcome this obstacle by using a propensity score to match surgically treated patients with conservatively treated controls sharing the same baseline characteristics. Although the resulting groups were balanced, the cases and controls may still have had significant differences in pairwise comparisons.

Unfortunately, we lack long-term functional outcome data for these patients. In addition, our propensity score analyses would have benefited from a larger sample, as the numbers of surgically treated patients were rather low and the baseline differences between the surgically and conservatively treated patients posed difficulties in finding properly matched patients.

6.8 Future prospects in ICH treatment and research

While the treatment options for ischaemic stroke have seen enormous progress during the last years, treatment of ICH has not evolved much in the last decades. Multiple large-scale randomised controlled studies (RCTs), the best available means to compare two treatments with minimal bias, have been conducted on treatment of ICH patients. Very few treatment options, including surgical treatment and haematoma evacuation, have shown to have a significant effect on mortality in RCTs. Current guidelines support rapid neuroimaging, medical treatment of clinical seizures, blood pressure lowering, treatment in specialist acute stroke unit, use of intermittent pneumatic stockings to prevent deep

venous thrombosis, and multidisciplinary rehabilitation.

Since very limited treatment strategies exist after the haemorrhage has occurred, the key to minimising ICH-related global disease burden is prevention. As the incidence of ICH has increased especially in low- and middle-income countries, it is important to encourage the use of antihypertensive medication and to facilitate access to primary and preventive health care in developing areas. Large regional disparities exist in access to neurologists even in wealthy countries, let alone less developed communities.

Instead of creating new prognostic scores for ICH, the stroke community should be aware of the risk of self-fulfilling prophecies and hasty decisions to withdraw care in patients with a suspected grim prognosis, e.g. patients with ICH-related hydrocephalus. The prognostic scores can be used to complement clinical decision-making, but they should be used with caution.

One possibility to search for the optimal strategy for treatment of intracerebellar haemorrhages and to assess the futility of care would be to measure the long-term survivors' health-related quality of life. Also useful would be to compare the outcome of surgically and conservatively treated patients in a large, multicentre propensity-matched case-control study.

Strategies to minimise ICH-related oedema, limit haematoma expansion, and decrease the occurrences warrant more research. As the aetiological classification is probabilistic by nature and tissue samples are seldom gathered, the definitive haemorrhage aetiologies are still largely unknown. Genome-wide analysis of single-nucleotide polymorphisms associated with CAA or hypertensive microangiopathy could shed light on the pathogenesis and facilitate the prevention of ICH. In addition, finding new drug molecules that could improve the removal of iron breakup products, thus helping to decrease cerebral oedema is of high importance, as are studying immunological reactions in the haematoma and surrounding brain after the ICH has occurred.

7 CONCLUSIONS

1. The best tools for mortality prognostication after ICH were NIHSS score for estimation of in-hospital mortality, and ICH-FOS score for 3- and 12-month mortality. Many of the scores shared similar point assignments, derived from the original ICH score. Hydrocephalus has been found to be a significant predictor of poor outcome, but it was not included in any of the scores. Prognostic scores may be helpful in scientific work, e.g. as inclusion criteria for prospective trials, but clinicians should be aware of the risks associated with possible self-fulfilling prophecies.

2. Surgical treatment of intracerebellar haemorrhage was not associated with better short- or long-term survival than conservative management, although it is probable that surgical treatment did succeed in preventing mortality in patients who otherwise would have died. Functional outcome of the surviving patients remained worse after surgical treatment than after conservative management. Current treatment guidelines support surgical treatment in patients with large intracerebellar haemorrhages and declining level of consciousness. However, the outcomes after surgery may not be as good as we neurosurgeons tend to think, and that the long-term functional outcome needs further studies because of the rather pessimistic short-term functional outcome and high long-term mortality.

3. Surgical treatment of ICH-related hydrocephalus was beneficial and in comparison to conservative management, it was associated with a substantially lower in-hospital and 3-month mortality. The hydrocephalic patients had a strikingly high in-hospital and 3-month mortality. As no good guidelines exist on when to treat ICH-related hydrocephalus or to insert an EVD, the treatment decisions are always made case-by-case. In the propensity score analysis, surgical treatment of ICH-related hydrocephalus was associated with a 50% reduction in mortality. This raises the question of whether the decision not to offer surgical treatment to hydrocephalic ICH patients could be a self-fulfilling prophecy.

4. In young adults, ICH evacuation was clearly associated with a decrease in mortality when compared with conservatively treated patients. In addition, the total 3-month mortality was 16.9%, significantly lower than the mortality in all ICH patients. Increasing symptom severity, infratentorial location, hydrocephalus, radiological herniation, and presence of multiple haemorrhages were associated with a higher 3-month mortality. Although not generalizable to the whole population, our results support ICH evacuation in selected young adult patients.

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Intracerebral haemorrhage (ICH) is a deadly subtype of stroke with an average 12-month mortality exceeding 50%. The most common causes for ICH include hypertensive microangiopathy, amyloid angiopathy, antithrombotic or anticoagulant medication, or systemic diseases. Despite advances at other frontiers of stroke treatment, treatment options for ICH are limited. Neurosurgical treatment for ICH has been discussed in recent multicentre studies, but no definitive answer of its utility has emerged.

Age, ICH volume and location, and extent of ventricular haemorrhage among other factors affect the prognosis after ICH. We studied the different prognostic scores for ICH to find the best tool for estimation of the risk of death after ICH. One of the best known is the ICH score, published in 2001.

In addition, we studied the effect of neurosurgical treatment (1) in patients with intracerebellar haemorrhage; (2) in patients with ICH-related hydrocephalus; and (3) in young adults in an observational, retrospective analysis of consecutive ICH patients admitted to Helsinki University Hospital during a five-year period.

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